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EVALUATION OF THE DANGERS OF REPEATED ADMINISTRATION OF SULFADIAZINE AND SULFATHIAZOLE IN CHILDREN

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WITH the widespread administration of the sulfonamide drugs, studies of untoward reactions become of great significance. The increased use of these drugs for very minor illnesses and even for prophylactic purposes makes crucially important the evaluation of the risks of "acquired sensitivity." A number of observers[1-8] have reported that patients who have received one course of the sulfonamides, with or without reactions, may develop febrile reactions at the onset of the second course. Lyons and Balberor,[1] studying only patients free of toxic symptoms during the initial course of sulfathiazole, reported severe immediate febrile reactions in 36 per cent of fifty-three adults receiving the drug a second time. It has been stated[2] that the occurrence of an immediate reaction, that is, a febrile reaction within the first day, almost invariably means that the patient has had previous contact with the drug. It is obvious that if the risk of such sensitization of a patient is considerable, the use of this extremely valuable therapeutic agent for minor illnesses or for prophylaxis may be quite unjustified, since it may prevent its lifesaving effect in future emergencies.

The purpose of this communication is to report an investigation of the incidence of acquired sensitivity in children.

One hundred and seventy-seven children were observed who had had more than one course of either sulfathiazole or sulfadiazine and who had had no reaction during the first course.

Eighty-six had been given sulfathiazole. Of these, forty-seven received the drug on two or more occasions for therapeutic reasons, very frequently the recurrence of bronchopneumonia, and the remaining

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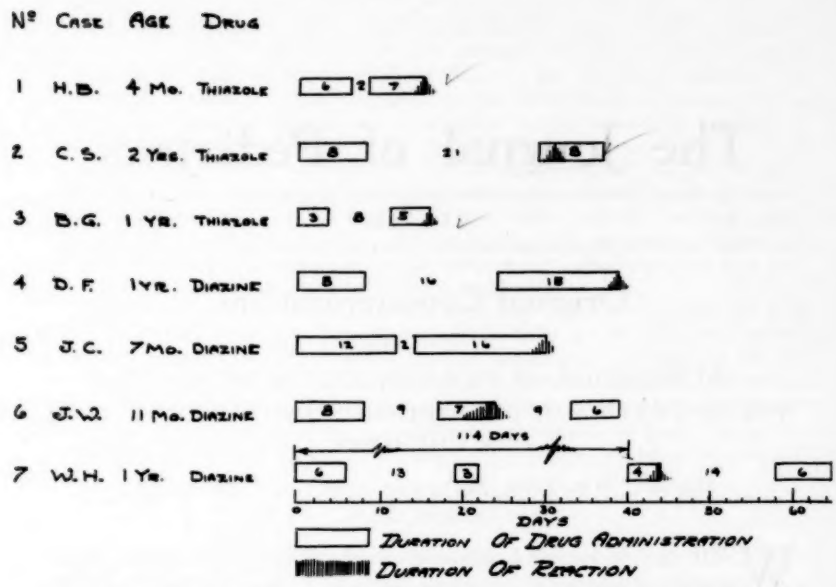
Nº Case Age Drug
1 H.B. 4 Mo. Thiazole
2 C.S. 2 Yrs. Thiazole
3 B.G. 1 Yr. Thiazole
4 D.F. 1 Yr. Diazine
5 J.C. 7 Mo. Diazine
6 J.W. 11 Mo. Diazine
7 W.H. 1 Yr. Diazine
114 Days
Days
Duration Of Drug Administration
Duration Of Reaction

Fig. 1.—Shows the type of response in the seven (of the 177) children developing reactions during the readministration of the sulfonamide drugs. All were free from reactions during the first course. Note that none of them developed the typical immediate type of reaction. The earliest response occurred on the second day (Case 2). In the others, fever appeared on the third, fourth, fifth, seventh, fourteenth, and fifteenth days. In Cases 6 and 7 the children received a third course without ill effect.

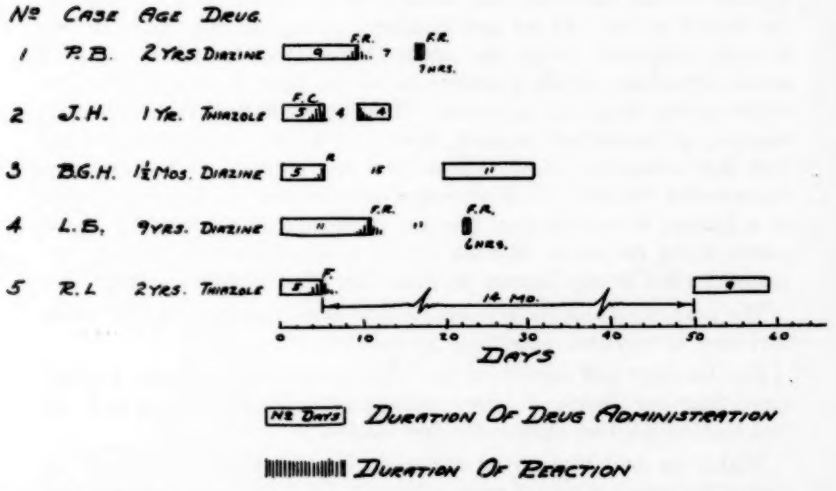

Fig. 2.—Shows the type of response occurring during the readministration of the sulfonamide drugs to five children who had had reactions in the initial course. Three children, Cases 1, 2, and 4, showed an immediate type of reaction, with rash and fever developing within eight hours. In Cases 3 and 5 the children showed no reaction. Note that in the child in Case 2 the drug was continued for four days despite the initial reaction. The child's temperature dropped to normal by the third day, remained normal thereafter. F., Fever; R, rash; C., conjunctivitis.

thirty-nine were given sulfathiazole deliberately for the purpose of this study, although they were, at the time, afebrile and free from active infection.

Ninety-one had been given sulfadiazine on more than one occasion, and of these, forty-one were given the drug a second time for study purposes at a period when they were well.

A small group of five children was observed who likewise had received either sulfathiazole or sulfadiazine on two occasions but all of whom had suffered a reaction during the initial course.

The ages of the children studied ranged from 10 days to 12 years. Eighty per cent were over 1 year of age and 54 per cent were over 2 years of age.

There were wide variations in the duration of the period of administration of these drugs. The initial course varied from two to forty-two days. The second course ranged from one to twenty-four days' duration. Thirteen of the children received more than two courses of the drugs, one being treated with sulfathiazole on six separate occasions. The time intervals between the first and second course ranged from one day to one and one-half years. It has been reported[1] that a period of from nine to twelve days must elapse before a patient can become sensitized. In over 75 per cent of our cases the time interval between the first and second course was more than seven days, and in all more than twelve days elapsed between the beginning of the first course and the end of the second.

In almost all cases the dosage was ½ gr. per pound initially, followed by a dosage of ¾ to 1 gr. per pound for each twenty-four hours during the course of administration.

There is sometimes doubt as to the significance of fever occurring during treatment with the sulfonamides, and it becomes difficult to determine whether an observed fever is a result of the infection being treated or is actually a reaction to the drug. For the purposes of this study, we have included questionable cases as drug reactions.

RESULTS

Seven of the 177 children studied (4 per cent) were found to have a febrile reaction during the second administration of the agent, three with sulfathiazole and four with sulfadiazine. Only one of the reactions occurred in the group of children who were given the drug for study purposes.

Of these seven patients (Fig. 1), none developed the typical "immediate" febrile response which has been described,[1] and none developed any rash. One developed fever at the close of the second day, the others on the third, fourth, fifth, seventh, fourteenth, and fifteenth days, respectively. In two of these the temperature fell to normal within two days, although the drug was continued for several days more. In the others the fever subsided only after the drug was stopped. Two of

the patients developing a febrile response were given a third course of the drug. No reaction occurred in either child.

In the small series of five children who had shown reactions during the first administration of a sulfonamide and were given the drug a second time, two had no reaction, but the remaining three developed an immediate type of febrile response with fever and rash within eight hours after the initial second dose (Fig. 2). One of these latter cases (Case 2) is interesting in that despite the rather severe initial reaction, the drug nevertheless was continued for four days. The child's temperature remained elevated on the second day but was normal thereafter. He showed no other ill effects.

DISCUSSION

The occurrence of seven reacting cases in 177 receiving a second course of sulfonamide therapy gives an incidence of four per cent, which is within the 2 to 10 per cent generally reported for reactions occurring during initial treatment.[9-11] There is, therefore, little evidence of an increased incidence of reactions during a second course, and only the one patient who developed his reaction as early as the second twenty-four hours after readministration might be considered an example of acquired sensitivity.

Whether or not the discrepancy between our figures and those previously reported is a result of our working exclusively with children is open to speculation. Certainly, it is common observation that children, particularly infants, tolerate chemotherapy better than most adults, despite the proportionately larger amounts of drugs given to children.

Our studies indicate that the use of the sulfonamides in children does not appear to predispose to the development of reactions on readministration of the drug. It is to be hoped that fear of sensitizing a child to a sulfonamide will not prevent the judicious use of chemotherapy in cases where the drug is thought to be of value. History of previous reaction to the sulfonamide group should, however, caution one to readminister the drug with the greatest care, as the likelihood of recurrence of toxic symptoms in this group is much greater.

SUMMARY

1. One hundred and seventy-seven children were given a sulfonamide drug during two or more courses and had no reaction during the first course. Eighty-six were given sulfathiazole; three developed febrile reactions, none within the first forty-eight hours. Ninety-one were given sulfadiazine; four developed febrile reactions, only one within the first forty-eight hours.

2. In the total of seven cases (4 per cent) exhibiting reactions to these two drugs, fever appeared first on the second, third, fourth, fifth, seventh, fourteenth, and fifteenth days, respectively. It is suggested

these febrile responses were toxic reactions to the drug that might have occurred at any time and had no clear relation to previous drug therapy.

3. Two of the seven children with initial reactions were given both a second and a third course of the drug without reaction.

4. An "immediate" type of febrile reaction occurred during a second course of sulfonamides in three of five children who had had reactions during a first course.

5. Our studies show that "sensitization" to sulfathiazole or sulfadiazine is not common or frequent in children, but that the occurrence of one reaction greatly increases the probability of future reactions.

6. Children who developed toxic symptoms during the first administration of the drug should be given the drug only with caution and close observation.

ADDENDUM

Since this paper was submitted, we have encountered four additional children in whom reactions developed during the first administration of a sulfonamide, five with sulfathiazole, and nine with sulfadiazine. After an interval of from four to ten days, each child was given a repeat trial dose of the corresponding drug. Eight of the children developed an "immediate" type of reaction, high fever and rash, occurring within eight hours after administration of the initial repeat dose. No reactions were noted in the remaining six.

Four of the children who showed an "immediate" response to sulfadiazine were later given a trial course of sulfathiazole. Only one developed a reaction. This latter child was subsequently given sulfapyridine without precipitating a reaction, although the child a week later did develop a mild leucopenia from which he recovered while receiving sulfapyridine.

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MENARCHEAL AGE AND THE HEIGHT, WEIGHT, AND SKELETAL AGE OF GIRLS AGE 7 TO 17 YEARS

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THIS report is concerned with the interrelationships of certain maturational indicators, namely, chronologic age at menarche, assessments of skeletal maturation, and standing height and body weight, together with their annual increments. No one of these indicators may be considered an entirely satisfactory criterion of maturation. It has been recognized that the age of first menstruation may have a different significance for different individuals. This aspect has been described by Greulich:[6] "The marked irregularity of the early menstrual cycles of girls should make one reluctant to attribute to the menarche itself the importance as a criterion of maturity which is commonly ascribed to it by writers on adolescence; for it seems probable that some of the same factors which are responsible for the marked irregularity of the early menstrual cycles in girls can operate to advance or retard the occurrence of the menarche itself."

"It would seem best, therefore, to regard the menarche as neither a dependable criterion of maturity nor as necessarily the expression of any narrowly circumscribed stage of sexual maturation. It is rather the reflection of a physiological state which may occur at different times during the puberal period in different individuals and which usually precedes by a considerable interval the attainment of the capacity to reproduce."

Menarche, then, is a variable not only in time of its occurrence, but also in its physiological significance; it is used here as the criterion (the independent variable) of maturity in the absence of any more satisfactory indicator.

It has been recognized that standing height and body weight and the annual increments in these measures bear relationships during the growing years to menarcheal age; these relationships have been well described, notably by Boas,[2, 3] Shuttleworth,[9] and Richey.[8] Insofar as these relationships are concerned, the data presented here do little more than substantiate with data derived from a different population sampling the findings they reported. It is well known that the variabilities of these measures increase during the premenarcheal years, that is, the variabilities of whole populations increase. These variabilities differ during successive stages of the growth cycle and they differ among selected groups of the population during any one stage of the growth cycle, as for example, the prepuberal stage. This "uneven rapidity with

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which children pass through the period of development," as Boas[3] expressed it, makes it possible to describe relationships among maturational indicators, but it does not permit the successful application of generalized norms of quantitative data to the rating of individuals.

That age ratings of skeletal maturation are related to menarcheal age has been demonstrated graphically by Shuttleworth.[9, 10] He concluded that since "the growth curve (skeletal age) for girls in general must be a straight line from birth to age 197 months at which point growth must abruptly cease . . . contrasts between early and late maturing groups of girls can only indicate that their growth patterns are different, while completely concealing the true nature of the differences."[10] "Such a curve by its very nature cannot represent true accelerations or decelerations of growth. At a given age it can only indicate whether one group is more advanced than another. Over a given age period it can only indicate whether one group is advancing faster than another."[9] "The estimated skeletal ages are entirely satisfactory for the purpose of cross-sectional and correlational studies, but they are wholly inadequate for longitudinal and developmental studies."[10] "The differences at each age (in average skeletal age of eight menarcheal age groups) in average skeletal development are unusually clear and regular."[9]

That it is impossible to derive a "growth curve" of the skeleton or of any of its parts from assessments of skeletal maturation expressed in age ratings is clear. Such assessments have never been intended for that purpose. It is the intention of users of the qualitative method of estimating skeletal maturity to base their assessments on skeletal changes which are independent of growth or change in size. Ideally, a skeletal age assessment would be a rating of simple maturity, uncomplicated by the growth factor. It is true, however, that the assessor, when using the roentgenographic comparison scale, is confronted with roentgenograms of areas which increase in size with advancing age, and to this change in size he cannot be at least subjectively unaware. So it is undoubtedly inevitable that, in the estimate of skeletal maturation, growth enters to some unknown extent. Conceptually the maturation process differs from the growth process and changes in skeletal development are, by observation, of a different nature from changes in size. It was Todd's conclusion that: "Maturation is far less subject to fluctuations in progress than growth. In robust, healthy children of good constitution it is a time-keeper of great reliability."[13] Age ratings give no clue to the specific changes taking place, either qualitative or quantitative. The concept of skeletal maturation as a "time-keeper," however, makes age ratings reasonable expressions to use in charting a child's course through time to maturity.

Age ratings of standing height and body weight are commonly used. They are unsatisfactory because stature and weight are themselves quantitative variables at maturity and because the terminal measurements

of these variables are not known in advance. Height-weight-age tables are unsatisfactory for the further reason that the height-weight correlation is not high enough for efficient individual prediction of one measure from the other,[11] although the correlation is high enough during the growing years for group predictability of considerable efficiency. Moreover, users of height-weight-age tables generally do not take into account the fact that at premenarcheal ages early maturing girls, as a group, are not only taller and heavier than late maturing girls, but their weight-for-height is also greater. Even had their greater weight for height not been shown empirically, as for example, by Richey[8] ("One girl of average height may be as much as 20 per cent heavier than another of the same age and height, yet both may be of average weight for their respective maturity groups"), it could readily be inferred from the characters of the weight curve (accelerating increments from about 3½ years of age until after menarche) and the height curve (decelerating increments from about 1 year of age to about the second year preceding menarche). This is an important factor in the evaluation of over- and underweight by use of tables. Furthermore, to know that a child rates "a year" in retardation or "a year" in advance of the average child of his same chronologic age according to a height-age standard is not to know how far the child has progressed toward his own mature height. A child who is accurately assessed in skeletal maturation one year in advance of the norm for his chronologic age is known to have progressed toward his own mature status farther than the central tendency child. According to Todd,[13] "Protracted or repeated ill-health, starvation or unhygienic conditions of life however do influence its [maturation's] progress and, if severe enough, may cause profound disturbances of pattern." The advanced child and the average child will arrive at the same destination, maturity, but the skeletally more mature child, barring such disturbances, may be expected to arrive there earlier.

To date, no treatment of height and weight data has resulted in a timetable exactly comparable with skeletal age standards, a timetable by which a child's developmental status and progress can be meaningfully rated in relation both to his own and to those of other children. The height-age and weight-age and height-weight-age tables fail in this respect, because, as has been stated, the absolute values in which height and weight are determined are themselves variables at the mature level; a tall 11-year-old girl may receive an adult rating when assessed by a height-age table although her own mature status may not be reached for several years.

A new height-weight-age rating technique has been presented recently by Wetzel.[14] His grid and auxodrome schedule are tools devised to serve many purposes, one of which is the assessment of maturational level. It is only with this aspect of his method that these comments are concerned. He states that his "developmental age" is an adequate substitute for skeletal age in the assessment of maturation: "This [a subject's de-

velopmental age] is obtained at once by reading the age at which the 67 per cent norm intersects a given developmental level. For example, the child whose level was previously stated to be 100 at 8.35 years by actual age is said to possess a developmental age of 11.6 years. Similarly, a level of 130 attained at 15.3 years corresponds to a developmental age of 13.7 years. The former child is advanced, the latter retarded in development" (p. 1192). ". . . Two subjects both of whom have arrived at level 100, no matter how or in which channel, are specifically to be considered as being on the same developmental level" (p. 1190). "This method of assessing development is comparable in some respects to, and serves the purpose of, determinations of skeletal age. It is, however, much simpler, entirely objective, less time consuming, and less expensive. In short, it avoids the disadvantages connected with roentgenologic determinations of skeletal age" (p. 1192).

In Table I, as an example of the application of Wetzel's technique to the assessment of maturity, are ratings of two Brush Foundation Regular Series girls.

TABLE I

	NO. 3430	NO. 3245	DIFFERENCE
Chronologic age	144 mo.	96 mo.	48 mo.
Wetzel's developmental level	101	100.5	0.5
Wetzel's developmental age	127.5 mo.	126.5 mo.	1 mo.
Weight/Height index	24	25	1
Height	1,443 mm.	1,379 mm.	64 mm.
Brush Height-Age (1936 standards)	129 mo.	115 mo.	14 mo.
Weight	76 lb.	77 lb.	1 lb.
Brush Weight-Age (1936 standards)	120 mo.	121 mo.	1 mo.
Skeletal age (1935 standards)	162 mo.	101 mo.	61 mo.
Months before menarche	9 mo.	45 mo.	36 mo.
Chronologic age at menarche	153 mo.	141 mo.	12 mo.
Skeletal age at menarche	170 mo.	159 mo.	11 mo.
Wetzel's developmental age at menarche	135 mo.	>192 mo.	>57 mo.

Thus, a 12-year-old girl, with skeletal age of 13 years, 6 months, nine months before her menarche, is at very nearly the same developmental level with very nearly the same developmental age as an 8-year-old girl, skeletal age 8 years 5 months, forty-five months before her menarche, 64 mm. shorter, but one pound heavier. These two girls, far from having arrived at the same maturational level, are equally "developed" in none of the measures considered other than body weight.

In Wetzel's developmental age, the 12-year-old girl is 16.5 months retarded, the 8-year-old girl is 30.5 months advanced. In Brush weight-age (1936) the 12-year-old girl is twenty-four months retarded, the 8-year-old girl is twenty-five months advanced. In skeletal age the 12-year-old girl is eighteen months advanced over her chronologic age standard, the 8-year-old girl is five months advanced over her chronologic age standard.

An auxodrome derived from the Brush Regular Series fiftieth percentiles in height and weight exceeds somewhat Wetzel's sixty-seventh

per cent norm. In consideration of this, the amount of advancement and retardation of these two subjects in Wetzel's developmental age agrees closely with their advancement and retardation in weight alone according to the age norms of weight for our Regular Series. Thus, a weight-age scale places the two girls in approximately the same relation to one another as Wetzel's developmental level scale and developmental age scale, in which height plays a relatively negligible part.

Wetzel's developmental age, then, represents almost exclusively an age-weight rating; it does not give a rating of the distance which a child has progressed toward her own maturity status. Brush girls begin to reach the adult level of the Wetzel developmental age schedule at age 11 years and therefore cannot be given age ratings thereafter. At ages 7 to 11 years, correlation coefficients between the Wetzel developmental age and the weight-height index range between 0.93 and 0.94 for Brush Regular Series girls.

SUBJECTS AND DATA

This report is based upon an analysis of the records of 200 girls of the Brush Foundation Regular Series. All Regular Series girls whose first menstruation has occurred are included, the occurrence of the menarche having been the only criterion of selection. The children of the Regular Series are, as a group, from families above the average in economic status; they have been referred by their pediatricians or family physicians as free from gross physical and mental defect; most of them have participated in the Brush measuring program for several years, and the greater number of them are of North European ancestry. Between 10 and 12 per cent (the proportion varies slightly with different age groups) are Hebrew. They do not, then, comprise a group entirely homogeneous in any selective factor but are, to a more than average extent, free from economic, physical, mental and nutritional handicaps; they have parents and physicians who have continued their cooperation in the Brush program for, in some cases, as long as eleven years.

The Regular Series children have been taken into the measuring program at all examination ages from 3 months to 14 years of age. Of the 200 girls on whose records this study is based, 118 had their first examination in 1935 and following years at the ages of 10 years or older. These are the girls of the Adolescent Series. The remaining 82 girls had their first examinations at some age between 1 and 9 years. A total of 1,339 examinations have been used, a mean of 6.7 examinations per girl.

By an examination is meant a visit by a child at or near her birthday to the laboratory where she is measured anthropometrically, roentgenographed, and examined psychometrically. At this time a health history, covering the year since the child's preceding examination, is obtained. Included in the health history is a record of the date of the first menstruation. Menarcheal data collected in this way are subject to some

error. Most of the girls in this group have, however, been participating in the measuring program for several years, and it is known in advance of the menarche by the girl herself or her mother or other person responsible for giving the girl's health history that the date of this occurrence is important to the laboratory records.

Until 1941 standing height was measured by an anthropometer of the Martin design. Since July, 1941, this measurement has been read from a stadiometer. Age level constants of standing height for the sampling of 200 girls from 7 through 17 years of age appear in Table II. These constants are closely similar to those derived from the entire number of Regular Series girls. Body weight is read from a Fairbanks scale register with the child dressed in indoor clothing, without shoes. Age level constants of weight from 7 through 17 years of age are presented in Table II for the same sample.

TABLE II

MEANS AND STANDARD DEVIATIONS OF STANDING HEIGHT (MM.), WEIGHT (POUNDS) AND SKELETAL AGE (MONTHS), 7 TO 17 YEARS

CHRONOLOGIC AGE (YR.)	NUMBER	STANDING HEIGHT		WEIGHT		SKELETAL AGE	
		MEAN	SIGMA	MEAN	SIGMA	MEAN	SIGMA
7	64	1237.76	43.48	55.06	7.99	91.19	9.43
8	73	1301.15	47.51	62.90	9.79	103.86	9.15
9	79	1357.11	48.88	70.44	12.43	115.47	10.18
10	124	1414.66	58.67	79.12	13.81	128.21	10.37
11	159	1485.70	65.61	89.55	16.46	139.99	9.86
12	191	1551.62	66.65	102.45	19.02	150.65	9.90
13	178	1600.34	58.52	112.08	18.17	161.70	10.68
14	166	1631.37	56.11	120.71	18.49	174.39	11.96
15	134	1648.16	53.64	126.53	18.10	186.28	11.02
16	106	1654.50	54.96	129.86	18.58	195.50	10.18
17	65	1656.92	50.66	134.35	20.65	203.44	8.37

The assessments of skeletal maturation in terms of skeletal age ratings were made according to the Todd 1935 roentgenographic standards of six areas: the hand as presented in Todd's *Atlas of Skeletal Maturation (Hand)*,[13] the foot, elbow, knee, hip, and shoulder (unpublished).

A skeletal age rating represents an average of the assessments of the six areas or of as many as are assessable. Up to and including the age of 11 years, all six areas are included in the skeletal age ratings of all girls. At the age of 12 years, 4.71 per cent of the girls exceed in skeletal maturity the oldest elbow standard, and 1.05 per cent exceed the oldest foot standard and are unassessable in these areas. The standard ceiling is exceeded in no other area until the age of 14 years when 1.81 per cent of the knee roentgenograms are unassessable. By the age of 15 years, 5.22 per cent of the shoulder roentgenograms show a degree of maturity greater than the 16-year, 9-month shoulder standard and by the age of 17 years no roentgenogram of either foot or elbow can be assessed. At ages 15, 16, and 17 years the hip is the only area assessable for all subjects. In Table III are shown the number and proportion of the total

TABLE III

NUMBER AND PER CENT OF ROENTGENOGRAMS REACHING AND EXCEEDING THE OLDEST STANDARDS OF SIX AREAS: HAND, FOOT, ELBOW, KNEE, HIP, AND SHOULDER

CHRONOLOGIC AGE (YR.)	NUMBER	ASSESSED AT OLDEST STANDARD		EXCEEDING OLDEST STANDARD		ASSESSMENTS USED		AGE LIMITS OF STANDARDS (FEMALE)
		NUMBER	%	NUMBER	%	NUMBER	%	
Hand								
14	166	8	4.82	0	0.00	166	100.00	
15	134	22	16.42	17	12.69	117	87.31	3 to 195 months
16	106	27	25.47	41	38.68	65	61.32	
17	65	12	18.46	48	73.85	17	26.15	
Foot								
12	191	1	0.52	2	1.05	189	98.95	
13	178	11	6.18	13	7.30	165	92.70	
14	166	21	12.65	57	34.34	109	65.66	3 to 177 months
15	134	12	8.96	103	76.87	31	23.13	
16	106	4	3.77	96	90.57	10	9.43	
17	65	0	0.00	65	100.00	0	0.00	
Elbow								
11	159	2	1.26	0	0.00	159	100.00	
12	191	11	5.76	9	4.71	182	95.29	
13	178	23	12.92	49	27.53	129	72.47	
14	166	18	10.84	120	72.29	46	27.71	3 to 165 months
15	134	3	2.24	126	94.03	8	5.97	
16	106	1	0.94	105	99.06	1	0.94	
17	65	0	0.00	65	100.00	0	0.00	
Knee								
13	178	1	0.56	0	0.00	178	100.00	
14	166	12	7.23	3	1.81	163	98.19	
15	134	23	17.16	21	15.67	113	84.33	3 to 195 months
16	106	25	23.58	44	41.51	62	88.49	
17	65	10	15.38	50	76.92	15	23.08	
Hip								
17	65	1	1.54	3	4.62	62	95.38	3 to 225 months
Shoulder								
14	166	2	1.20	0	0.00	166	100.00	
15	134	4	2.98	7	5.22	127	94.78	
16	106	8	7.55	21	19.81	85	80.19	3 to 201 months
17	65	20	30.77	24	36.92	41	63.08	

number of roentgenograms which are assessed at the oldest standard of each area, number and proportion which exceed in maturity the oldest standard and are thus unassessable, and the number and proportion of roentgenograms used, including those assessed at the oldest standard.

This report includes a description and discussion of the results of the application of the Todd standards insofar as they relate to this study but is not purported to be a critique of the standards themselves. The possibility of improving upon the standards was recognized by Dr. Todd and others after the standards had been applied in assessing roentgenograms of our Regular Series children. The 1935 standards were derived from a large number of roentgenograms (3,657 male, 3,403 female), but

at that time only short series of consecutive examinations of Regular Series children had been made, and at some ages no examinations of Regular Series children had been made. Longer series are now available, and a sufficiently large number of roentgenograms of Regular Series children have been accumulated to obviate the necessity of using any supplementary population samplings as was done in the 1935 standardization.

Skeletal age ratings by the 1935 standards have been made by four assessors; from 1936 through 1938 assessments were made by both Dr. T. Wingate Todd and Dr. Carl C. Francis; in 1939 the assessing was done by Dr. Francis and Dr. David R. L. Duncan; in 1940, by Dr. Francis and Miss Clara Buehl; and in 1941 and 1942, by Miss Buehl. Of the 1,339 birthday examinations used in this report, Dr. Francis assessed the greater number. Many of Dr. Francis' ratings are his reassessments according to the 1935 standards (Todd's third revision of his original 1927 standards) of roentgenograms he had previously assessed according to the 1931 and 1934 standards.

The means of skeletal age at the chronologic age levels (Table II) for this series of girls agree very closely with the means of the total number of Brush Regular Series girls, not presented here. The excess of mean skeletal age over chronologic age from 7 to 16 years does not indicate that the group of 200 girls is a special sampling of our series; rather, it is a true indication of the tendency of our Regular Series children, both girls and boys, to rate above the 1935 standards in skeletal maturity. It is clear that the skeletal development norms selected by Dr. Todd in his standardization are considerably lower at most ages than the central tendencies of our Regular Series children.

A comparison (Table IV) of the percentage distribution of chronologic ages at menarche of Brush girls with like distributions of some other populations (from Shuttleworth[9]) shows that the girls in our series are characterized by an earlier menarcheal age central tendency. The mean menarcheal age of the Brush girls is 12.6 years, about six months earlier than that of the Harvard Growth Study girls[9] and about a year earlier than the means of the Chicago Laboratory School girls[1] and the New York Hebrew Orphan Asylum girls.[2]

For comparison with chronologic age at menarche, skeletal age at menarche has been determined by linear interpolation. For this, 187 girls were available, thirteen subjects having lacked the examination either preceding or succeeding the menarche. There is a positive correlation between chronologic and skeletal ages at menarche; the r* between these variables is $+0.453 \pm 0.058$. Table V gives the means and ranges of interpolated skeletal ages for eleven menarcheal age groups, menarcheal ages having been grouped in six-month intervals from the lowest, 10 years to 10 years, 5 months, to the highest, 15 years to 15 years, 5 months. Menarche occurred most frequently in 39 cases in the interval from 12

*Correlation coefficient.

TABLE IV

COMPARATIVE PERCENTAGE DISTRIBUTIONS OF MENARCHEAL AGES

CHRONOLOGIC AGE AT MENARCHE	BRUSH FOUNDATION	HARVARD GROWTH[9]	CHICAGO LABORATORY SCHOOL[1]	HEBREW ORPHAN ASYLUM[2]	HORACE MANN	
					HEBREW[2]	NON-HEBREW[2]
10 yr. to 10 yr., 11 mo.	3.5	3.2	1.0	1.1	3.4	3.4
11 yr. to 11 yr., 11 mo.	27.5	12.1	7.6	9.7	13.8	12.7
12 yr. to 12 yr., 11 mo.	35.0	33.5	23.0	22.7	31.9	31.8
13 yr. to 13 yr., 11 mo.	27.0	36.3	35.3	31.9	27.6	30.9
14 yr. to 14 yr., 11 mo.	6.0	10.5	25.3	27.0	17.2	12.7
15 yr. to 15 yr., 11 mo.	1.0	3.2	6.0	7.6	5.2	6.8
16 yr. to 16 yr., 11 mo.	---	0.8	1.6	---	0.9	1.7
17 yr. to 17 yr., 11 mo.	---	---	0.2	---	---	---
18 yr. and above	---	0.4	---	---	---	---
Number	200	248	487	185	116	236
Mean (yr.)	12.6	13.0	13.5	13.5	13.1	13.1
Sigma (yr.)	1.1	1.1	1.1	1.1	1.2	1.2

TABLE V

MEAN SKELETAL AGE (INTERPOLATED) AT MENARCHE OF ELEVEN MENARCHEAL AGE GROUPS

CHRONOLOGIC AGE AT MENARCHE	NUMBER	MEAN SKELETAL AGE AT MENARCHE (INTERPOLATED)	RANGE SKELETAL AGE AT MENARCHE (INTERPOLATED)
10 yr. to 10 yr., 5 mo.	2	145.50	144-147
10 yr., 6 mo. to 10 yr., 11 mo.	2	149.50	149-150
11 yr. to 11 yr., 5 mo.	14	154.00	149-164
11 yr., 6 mo. to 11 yr., 11 mo.	35	155.91	149-165
12 yr. to 12 yr., 5 mo.	30	155.67	148-167
12 yr., 6 mo. to 12 yr., 11 mo.	39	156.46	146-170
13 yr. to 13 yr., 5 mo.	22	157.64	150-164
13 yr., 6 mo. to 13 yr., 11 mo.	29	160.93	146-171
14 yr. to 14 yr., 5 mo.	9	159.33	153-169
14 yr., 6 mo. to 14 yr., 11 mo.	3	164.33	155-174
15 yr. to 15 yr., 5 mo.	2	160.50	160-161

years, 6 months, to 12 years, 11 months; the mean interpolated skeletal age at menarche for these thirty-nine girls is 156.46 months, 0.5 month lower than the mean interpolated skeletal age of the entire group.

It is apparent from Table VI that chronologic age at menarche is about twice as variable as skeletal age; slightly more than half of the skeletal ages fall within ± three months of the mean, compared with 23 per cent of the chronologic ages. Only 3.7 per cent of the skeletal ages deviate from the mean by thirteen months or more, whereas 26 per cent of the chronologic ages show more than one year's deviation from the mean.

TABLE VI

COMPARISON OF MEANS AND VARIABILITIES OF SKELETAL AGE (INTERPOLATED) AT MENARCHE AND CHRONOLOGIC AGE AT MENARCHE

	CHRONOLOGIC AGE AT MENARCHE		CHRONOLOGIC AGE AT MENARCHE		SKELETAL AGE AT MENARCHE (INTERPOLATED)	
Number	200		187		187	
Mean	150.92		151.52		156.99	
Sigma	12.75		11.30		5.34	
Variability coef.	8.45		7.46		3.40	
Range	122-183 (61)		122-183 (61)		144-174 (30)	
	NO.	%	NO.	%	NO.	%
Mean ± 3 mo.	41	20.50	43	22.99	95	50.80
Mean ± 6 mo.	71	35.50	75	40.11	149	79.68
Mean ± 9 mo.	106	53.00	102	54.54	172	91.98
Mean ± 12 mo.	144	72.00	138	73.80	180	96.26
13 mo. and more from mean	56	28.00	49	26.20	7	3.74

The interpolated skeletal ages have a total range of 30 months and a standard deviation of 5.3 months compared with the 61-month range and 11.30-month standard deviation characterizing the chronologic ages. The occurrence of the menarche in this group of girls, then, can be defined by skeletal age within much narrower limits than by chronologic age.

The mean interpolated skeletal age at menarche for these 187 subjects is 156.99 months; the mean chronologic age at menarche for the same subjects is 151.52 months. It has been pointed out that the Regular Series girls tend to rate, on the average, several months in advance of the 1935 skeletal age standards. Had the standards been derived from roentgenograms of Regular Series girls, the means of skeletal age and of chronologic age at menarche would be expected to coincide at about 12 years, 7 months. The association between skeletal age and occurrence of the menarche was recognized by Dr. Todd early in his study of skeletal maturation. In 1930, when he had had available for study only cross-sectional data from heterogeneous school populations, he wrote: "The investigations conducted at Western Reserve University have resulted in definition of the skeletal features characteristic of so-called precocious and delayed maturation. These are responsible for the individual variation found in dates of epiphysial union and recorded in disorder in the textbooks. Comparison with the records of first menstruation date shows that by far the great majority of girls begin to menstruate when the roentgenographic record of their skeletal development registers an age of 13.5 to 14 years. A minority start in the previous six months or scatter over a wider range. Not the chronological age but the developmental age is significant in relation to menstruation."[12] The development of Regular Series girls tends to proceed at a more rapid rate than that of the unselected population. The several revisions of the standards which followed the original 1927 working standards were made in an upward direction so that the skeletal age at menarche of Regular Series girls centers around 13 years instead of 13.5 to 14 years.

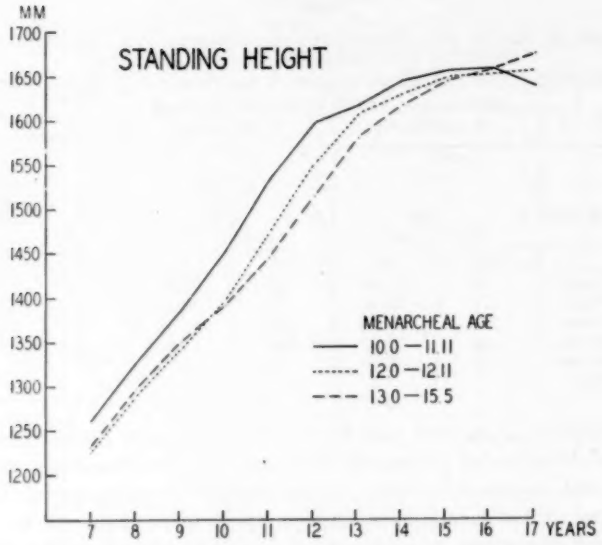

Fig. 1.—Mean standing height of girls 7 to 17 years of age in three menarcheal age groups.

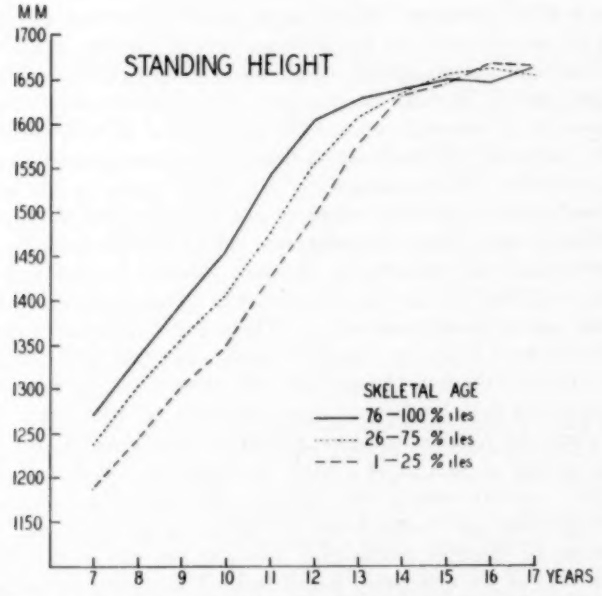

Fig. 2.—Mean standing height of girls 7 to 17 years of age in three skeletal age groups.

STANDING HEIGHT AND MENARCHEAL AGE

The means of standing height at ages 7 to 17 years are shown in Fig. 1 for three groups of girls whose chronologic ages at menarche are: first, between 10 years and 11 years, 11 months; second, between 12 years and 12 years, 11 months; and third, between 13 years and 15 years, 5 months. Small numbers at both age extremes and a lack of completely longitudinal data contribute to the irregularities which are apparent. It may be concluded, however, that through the premenarcheal years until adult stature is attained there is a definite tendency for girls with early menarches to be considerably taller than girls with late menarches. Fig. 2 shows the standing height means from 7 to 17 years for the same girls when arranged in three categories of skeletal age; first, those who rate between the seventy-sixth and one hundredth percentiles in skeletal age; second, those who rate between the twenty-sixth and seventy-fifth percentiles in skeletal age; and third, those who rate between the first and twenty-fifth percentiles in skeletal age. The tendency for girls of different developmental status to be differentiated in respect to standing height is marked; the divergence in height of the three groups of girls classified according to skeletal age is indeed greater from 7 years through 12 years than that of girls classified according to menarcheal age. Over this age range the mean height of girls whose skeletal ages fall among the upper 25 per cent of the group is invariably greater than that of girls whose skeletal ages fall in the middle 50 per cent interval, and the mean height of girls whose skeletal ages fall in the middle range is invariably greater than that of the girls in the lower 25 per cent of the skeletal age distributions.

WEIGHT, WEIGHT-HEIGHT INDEX, AND MENARCHEAL AGE

When the weight means from 7 through 17 years of age are obtained for three groups of girls—first, those with menarches between 10 years and 11 years, 11 months; second, those with menarches between 12 years and 12 years, 11 months; and third, those with menarches between 13 years and 15 years, 5 months—they show differences (Fig. 3) similar to height differences of the same three groups of girls. The weight central tendencies of girls whose skeletal ages fall first, within the seventy-sixth to one-hundredth percentile interval; second, between the twenty-sixth and seventy-fifth percentile interval; and third, between the first and twenty-fifth percentile interval (Fig. 4) are widely differentiated and remain at different levels through the age of 17 years. It is apparent that the weight relationships with both skeletal age and menarcheal age remain positive until a later age than do the height relationships.

It has been mentioned that an early menarche is associated with not only greater than average height and greater than average weight during the premenarcheal years, but also with greater weight for height. Furthermore, it has been pointed out that greater weight for height is inevitably an association of a rapid rate of growth owing to the growth

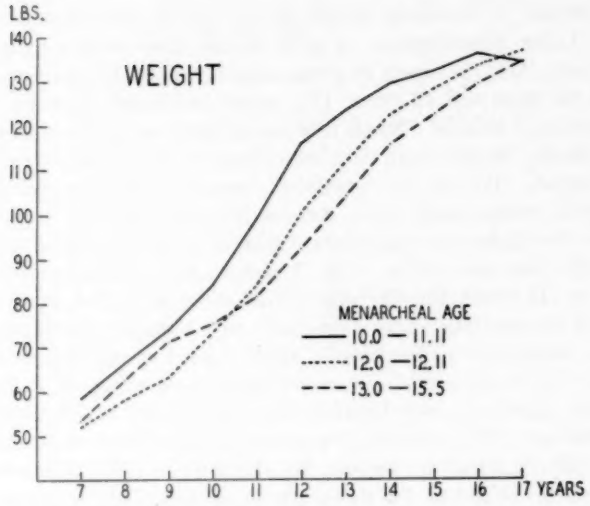

Fig. 3.—Mean weight of girls 7 to 17 years of age in three menarcheal age groups.

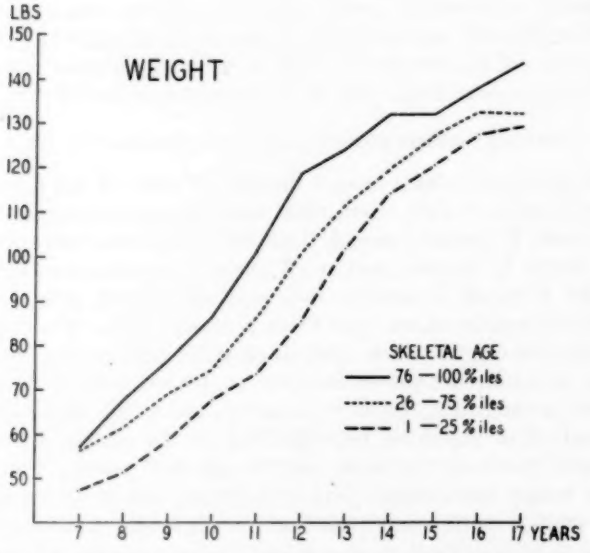

Fig. 4.—Mean weight of girls 7 to 17 years of age in three skeletal age groups.

curves characteristic of the two measures, a curve of accelerating increments in the case of weight, a curve of decelerating increments in the case of height until shortly, usually about two years, before menarche. The central tendencies of weight-height index from 7 to 17 years of age for the three groups of girls classified according to menarcheal age as before are shown in Fig. 5. The mean weight-height index of the girls with the earliest menarcheal ages is invariably greater than that of the girls in the other two groups from 7 years through 16 years of age. There are irregularities in the mean index of the middle and late groups, but from the age of 10 years through 17 years the index of the middle group is invariably greater than that of the group with late menarcheal ages.

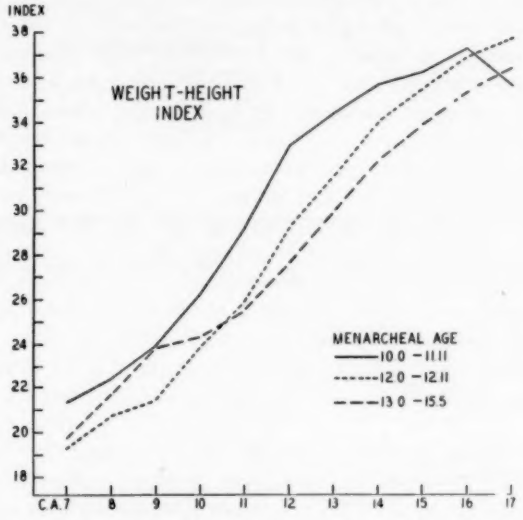

Fig. 5.—Mean weight-height index of girls 7 to 17 years of age in three menarcheal age groups.

SKELETAL AGE AND MENARCHEAL AGE

The same three groups of girls, those with early, average, and late menarches, are distinguished from one another by their mean skeletal age (Fig. 6) more consistently and regularly than by their height, weight or weight-height index. The skeletal age central tendencies of girls with an early menarcheal age are invariably greater than those of girls with an average menarcheal age, and the skeletal age means of girls with a late menarcheal age are invariably lowest of the girls in the three groups from 7 to 17 years of age.

ANNUAL INCREMENTS AND MENARCHEAL AGE

Standing Height Increments.—Fig. 7 shows the curves of mean annual increment in standing height of the girls in the three menarcheal age groups. Girls with menarches between 10 years and 11 years, 11 months have their greatest mean annual height increment between their tenth

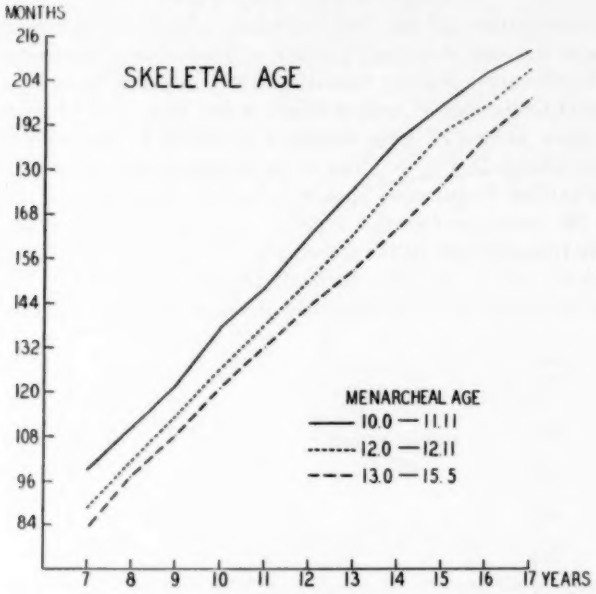

Fig. 6.—Mean skeletal age of girls 7 to 17 years of age in three menarcheal age groups.

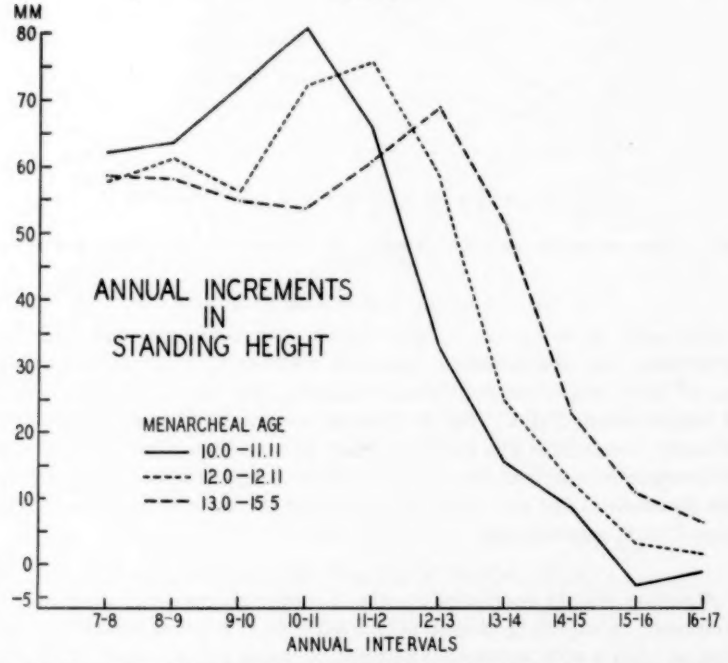

Fig. 7.—Mean annual increment in standing height of girls in three menarcheal age groups.

and eleventh birthdays; girls with menarches between 12 years and 12 years, 11 months have their greatest mean annual height increment between their eleventh and twelfth birthdays, and this increment is less than the greatest increment of the girls with early menarches; girls with menarches between 13 years and 15 years, 5 months have their greatest mean annual height increment between their twelfth and thirteenth birthdays, and this increment is less than the greatest increments of the other two groups.

When the annual height increments of eight menarcheal age groups are shown with the annual increments ending at the birthday before menarche plotted in the same vertical line (Fig. 8), the eight increment values appear, at the birthday before menarche, in perfect negative relationship to the menarcheal age; girls with menarches occurring at 10 years, 11 months and below show the greatest increment; girls with menarches at 14 years and above show the least increment; and the intermediate groups are characterized by decreasing increment with increasing menarcheal age in regular order.

This relationship between menarcheal age and stature increment was described by Boas,[2, 3] who summarized[4] his finding as follows: "These studies proved that when the maximum rate of growth is early, the whole growth proceeds at a rapid rate from the early years on, at least as far as our material permits us to follow it; the onset of the puberty spurt is early, its intensity great, its duration short. Conversely, when the period of maximum rate of growth is late, its intensity is slight, its duration long. This is expressed by the values of the maximum rates of growth which are low for those who reach maturity late, high for those who reach it early."

With but one exception, the greatest mean annual height increment in the girls of the eight maturity groups occurs during the year ending at the birthday before menarche; the exception is the group with menarches at 14 years of age or later, and the greatest annual height increment for the girls in this group occurs during the year ending at the second birthday before menarche. The greatest increment never occurs after the menarche; this is not only evidenced by group means, but is also descriptive of all individuals of this series for whom the age of maximum increment can be determined. The average girl experiences her greatest annual height increment during the year preceding the year in which menarche occurs. The greatest annual increment does occur, however, during the year of menarche; it does occur during the second year preceding menarche and, because our measurements are made only once annually, the premenarcheal maximum increment may be spread over a two-year period. The interval between the year of maximum increment and the menarche tends to be longer in the case of girls with late menarches than in the case of girls with early menarches. Some girls with late menarches seem, at least from measurements made only at the birthday, to experience little or no premenarcheal acceleration; the al-

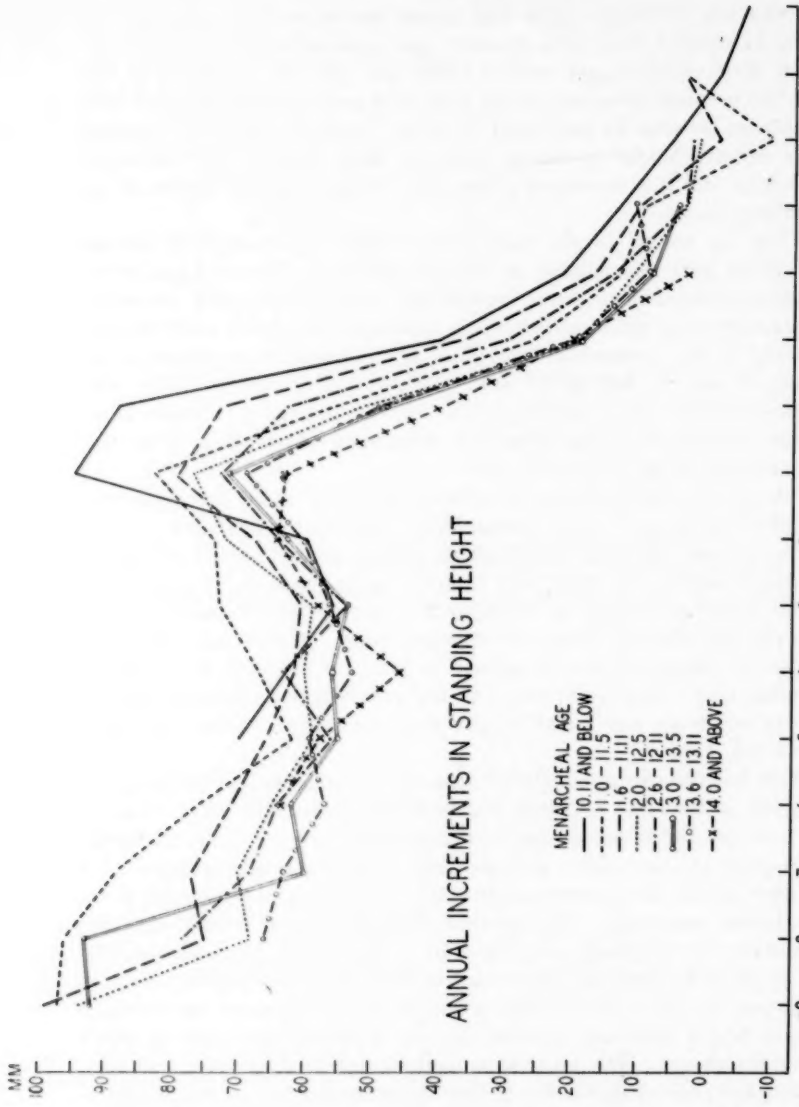

Fig. 8.—Mean annual increment in standing height of girls in eight menarcheal age groups with the increments ending at the birthday before menarche plotted in the same vertical line.

most linear growth rate of childhood seems to extend far into the teen ages and to level off abruptly.

Weight Increments.—From the curves of annual increment means in weight for the same three menarcheal age groups (Fig. 9) it appears that the period of maximum increment in weight is longer than the period of maximum increment in stature. The weight increments for the years

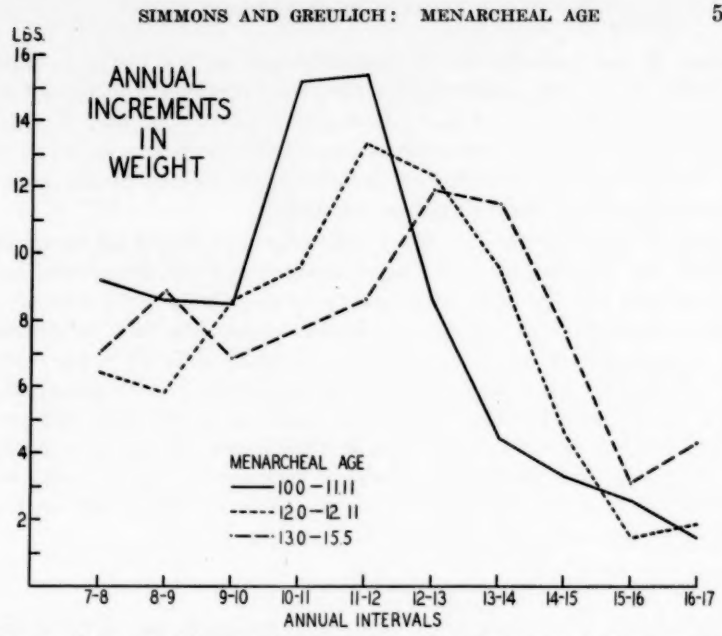

Fig. 9.—Mean annual increment in weight of girls in three menarcheal age groups.

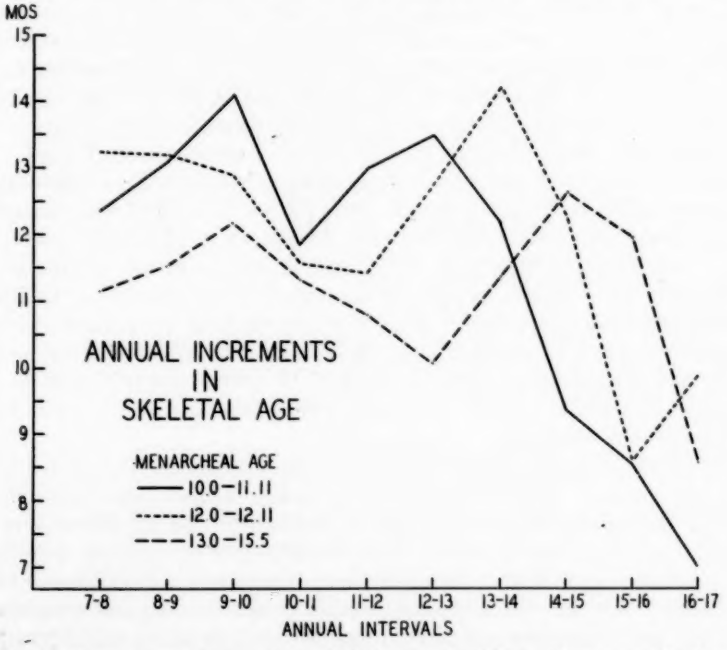

Fig. 10.—Mean annual increment in skeletal age of girls in three menarcheal age groups.

ending at the birthday before menarche and at the birthday after menarche tend to be similar. The magnitude of maximum increment is, as in stature, in direct negative relationship to menarcheal age. The decrease in increment following the maximum spurt is not as severe as in the case of stature; the falling off in increment is greatest for the group experiencing the greatest maximum increment.

Skeletal Age Increments.—The curves of annual increment means in skeletal age for the girls in the early, average, and late menarcheal age groups show that the increments tend to range from 10 to 14 months of skeletal age with irregularities within this range (Fig. 10). A falling off in mean increment occurs after the thirteenth birthday in the early maturing group, after the fourteenth birthday in the average group, and after the fifteenth birthday in the late maturing group. This decrease occurs about two years later than the decrease in stature increment, about one year later than the decrease in weight increment. It may be assumed that the skeletal age increment curves are, to some considerable but not definitely determined extent, artifacts of the standards.

CORRELATIONS

Correlation coefficients (r's) between chronologic age at menarche and skeletal age at ages 7 years through 17 years range from –0.46 (8 years) to –0.86 (14 years); they are all significant. The lowest is sufficiently high for fair group predictability; the highest and others approaching it indicate efficient group predictability. Correlation coefficients (r's) between menarcheal age and standing height from 7 years through 17 years range from –0.28 (7 years) through –0.56 (12 years) to +0.02 and +0.20 (16 and 17 years). The correlations at ages 7, 8, 14, 15, 16, and 17 years are not significant. Correlation coefficients between menarcheal age and weight from 7 years through 17 years range from –0.11 (9 years) through –0.54 (12 years) to –0.08 (17 years). The correlations at ages 7, 8, 9, 16, and 17 years are not significant. From 13 years through 16 years of age the correlations of weight with menarcheal age are higher than the correlations of stature with menarcheal age. The correlation coefficients between menarcheal age and the weight-height index range from –0.02 (9 years) through –0.47 (12 years) to +0.05 (17 years). The correlations at ages 7, 8, 9, 10, and 17 years are not significant.

From 10 years through 13 years of age the correlations of menarcheal age with height, with weight, and with weight-height index are sufficiently high to indicate fair group predictability. No significant relationship is found between menarcheal age and height or weight or weight-height index at 16 and 17 years of age. There is a real difference in the menarcheal age forecasting efficiencies of skeletal age and standing height, the menarcheal age-skeletal age correlations being significantly higher than the menarcheal age-stature correlations at the age of 7 years

TABLE VII

CHRONOLOGIC AGE (YR.)	d/σ_d	CHRONOLOGIC AGE (YR.)	d/σ_d
7	2.73	13	8.03
8	2.04	14	9.29
9	1.62	15	8.69
10	2.98	16	7.36
11	3.29	17	6.86
12	6.02		

TABLE VIII

CORRELATION COEFFICIENTS (r) BETWEEN MENARCHEAL AGE AND SKELETAL AGE, STANDING HEIGHT AND WEIGHT, FROM 7 TO 17 YEARS

CHRONOLOGIC AGE (YR.)	NO.	SKELETAL AGE MENARCHEAL AGE (r)	STATURE MENARCHEAL AGE (r)	WEIGHT MENARCHEAL AGE (r)
7	64	−0.514 ± 092	−0.279 ± 115	−0.201 ± 120
8	73	−0.458 ± 092	−0.291 ± 107	−0.129 ± 115
9	79	−0.480 ± 087	−0.352 ± 099	−0.113 ± 111
10	124	−0.588 ± 058	−0.418 ± 074	−0.290 ± 082
11	159	−0.685 ± 042	−0.550 ± 055	−0.453 ± 063
12	191	−0.798 ± 026	−0.557 ± 050	−0.535 ± 052
13	178	−0.849 ± 021	−0.375 ± 064	−0.427 ± 061
14	166	−0.856 ± 020	−0.150 ± 076	−0.297 ± 071
15	134	−0.826 ± 027	−0.044 ± 086	−0.241 ± 081
16	106	−0.780 ± 038	+0.015 ± 097	−0.214 ± 093
17	65	−0.726 ± 059	+0.200 ± 119	−0.078 ± 123

TABLE IX

CORRELATION COEFFICIENTS (r) BETWEEN SKELETAL AGE AND STANDING HEIGHT, BETWEEN SKELETAL AGE AND WEIGHT, AND BETWEEN STANDING HEIGHT AND WEIGHT, FROM 7 TO 17 YEARS

CHRONOLOGIC AGE (YR.)	NO.	SKELETAL AGE STATURE (r)	SKELETAL AGE WEIGHT (r)	STATURE WEIGHT (r)
7	64	+0.599 ± 080	+0.483 ± 096	+0.690 ± 065
8	73	+0.636 ± 070	+0.563 ± 080	+0.695 ± 060
9	79	+0.609 ± 071	+0.572 ± 076	+0.701 ± 057
10	124	+0.660 ± 051	+0.620 ± 055	+0.655 ± 051
11	159	+0.683 ± 042	+0.673 ± 043	+0.689 ± 042
12	191	+0.639 ± 043	+0.691 ± 038	+0.661 ± 041
13	178	+0.385 ± 063	+0.532 ± 054	+0.568 ± 051
14	166	+0.140 ± 076	+0.388 ± 066	+0.486 ± 059
15	134	−0.006 ± 086	+0.242 ± 081	+0.429 ± 070
16	106	−0.102 ± 096	+0.220 ± 092	+0.428 ± 079
17	65	−0.054 ± 127	+0.313 ± 114	+0.406 ± 106

and at 10 years through 17 years. The ratios of these correlation differences to their standard errors are in Table VII.

Table VIII gives the correlation coefficients of menarcheal age with skeletal age, with standing height, and with weight.

The correlation coefficients of skeletal age with standing height and with weight and of standing height with weight appear in Table IX. From 7 years through 11 years, skeletal age is somewhat more closely related to stature than to weight; from 12 years through 17 years,

skeletal age is somewhat more closely related to weight than to stature. From 7 years through 12 years, the skeletal age-stature r is 0.6; after 12 years the r drops abruptly to 0.38, 0.14, –0.01, –0.10, and –0.05. This decrease occurs at the same age, 13 years, as the decrease in the stature-menarcheal age relationship. The skeletal age-stature r's are significant from 7 years through 13 years; thereafter they are insignificant. The positive relationship between skeletal age and weight continues through the age of 17, as was shown graphically in Fig. 4, and although the r's between these variables decrease after the highest r of +0.69 at the age of 12 years, the decrease is more gradual than in the case of stature-skeletal age r's. This has been shown to be characteristic of the weight-menarcheal age relationship also. Weight-skeletal age r's are significant from 7 years through 15 years of age; thereafter they are insignificant. The correlations between skeletal age and the weight-height index increase from +0.36 at the age of 7 years to +0.61 at the age of 12 years; thereafter they decrease gradually, following the weight relationship, and remain positive through 17 years.

The stature-weight relationship is not constant throughout the age range 7 years through 17 years; the r's range between +0.655 and +0.701 from 7 years through 12 years; thereafter the r decreases to +0.406 at 17 years. No one of these correlations is sufficiently high for efficient individual prediction of one measure from the other; the highest indicates good group predictability, the lowest slight group predictability.

Girls grouped according to menarcheal age have been shown graphically to be diffentiated by both the time and intensity of premenarcheal maximum increment in standing height. Annual increments in standing height bear some relationship also to height status and to skeletal age. Over the prepuberal to postpuberal age range, however, the correlations of annual height increment with menarcheal age, with height status and with skeletal age vary in both direction and degree. The six intercorrelations among the four variables

13-year standing height
13- to 14-year standing height increment
13-year skeletal age
Menarcheal age

fall into two groups of three correlations each, one group of the quantity 0.3 and the other group of the quantity 0.8. The correlations of standing height at the age of 13 years with standing height increment from 13 to 14 years, with skeletal age at 13 years, and with menarcheal age are all at the 0.3 level. These correlations are significant but low.

13-year standing height with 13- to 14-year height increment	–0.340
13-year standing height with 13-year skeletal age	+0.385
13-year standing height with menarcheal age	–0.375

The three correlations among the variables, 13-year skeletal age, 13- to 14-year standing height increment, and menarcheal age are all at the 0.8 level.

13-year skeletal age with 13- to 14-year height increment		–0.809
13-year skeletal age with menarcheal age		–0.849
Menarcheal age with 13- to 14-year height increment	r	+0.764
	η	0.802

These three correlations are all significant and all indicate a high degree of group predictability. The correlation of 13-year skeletal age with menarcheal age (–0.849) is significantly greater than that of 13-year standing height with menarcheal age (–0.375), the d/σ_d being 8.03. The correlation of 13-year skeletal age with 13- to 14-year height increment (–0.809) is significantly greater than that of 13-year standing height with 13- to 14-year height increment (–0.340), the d/σ_d being 6.78.

The increment in standing height from 13 to 14 years is, then, nearly as highly correlated with menarcheal age as is skeletal age at 13 years. As an indicator of maturity status, standing height increment is less valid at earlier ages. The correlation (r) between menarcheal age and standing height increment is –0.136 at 7 to 8 years; it rises to –0.536 at 9 to 10 years and –0.627 at 10 to 11 years, drops abruptly to –0.043 at 11 to 12 years, and rises sharply to +0.648 at 12 to 13 years. Correlations of +0.6 to +0.7 are maintained through the 15- to 16-year increment. The curvilinearity of the relationship of 11- to 12-year height increment with menarcheal age is remarkable; the line of relation describes a $\wedge$-shaped curve, the correlation ratio being 0.663. Large increments are experienced by girls whose menarches occur between their twelfth and thirteenth birthdays; small increments are experienced by two distinctly different groups of girls, first, those who have had their maximum increment and are in the final decelerating phase of growth, or the early maturing group, and second, those who have not yet entered into the premenarcheal accelerating phase of growth, or the late maturing group. Although the correlation ratio of 0.663 is comparable in magnitude with the correlation coefficients –0.627 (10- to 11-year increment) and +0.648 (12- to 13-year increment) for practical purposes, the predictability is zero. Slight curvilinearity characterizes the lines of relation between menarcheal age and the 10- to 11-year height increment and between menarcheal age and the 12- to 13-year height increment.

The change in direction from negative to positive occurs also in the correlations of height increment with height status and of height increment with skeletal age with marked curvilinearity of the lines of relation when the direction is changing. The correlations of standing height status at the birthday with height increment over the succeeding year and of skeletal age at the birthday with height increment over the succeeding year for ages 9 to 13 years are given in Table X.

TABLE X

CHRONOLOGIC AGE	HEIGHT INCREMENT INTERVAL (YR.)	STANDING HEIGHT (r)	SKELETAL AGE (r)
9	9 to 10	+0.303	+0.450
10	10 to 11	+0.271	+0.365
11	11 to 12	-0.057	-0.031
12	12 to 13	-0.443	-0.753
13	13 to 14	-0.340	-0.809

TABLE XI

COMPARATIVE CORRELATION COEFFICIENTS BETWEEN MENARCHEAL AGE AND OTHER PHYSICAL MEASURES

CORRELATIONS WITH MENARCHEAL AGE	BRUSH (r)	HARVARD GROWTH (r)	CHICAGO LABORATORY SCHOOL (r)
Standing height at 8 years	-0.291	-0.308	
Weight at 8 years	-0.129	-0.210	
Skeletal age at 8 years	-0.458	-0.421	
Standing height at 12 years	-0.557	-0.500	
Weight at 13 years	-0.427	-0.496	
Skeletal age at 13 years	-0.849	-0.713	
Standing height increment 10 to 11 years	-0.627	-0.595	
Weight increment 10 to 11 years	-0.537	-0.500	
Skeletal age increment 10 to 11 years	-0.110	-0.322	
Standing height increment 13 to 14 years	+0.764	+0.679	
Weight increment 13 to 14 years	+0.361	+0.336	
Skeletal age increment 15 to 16 years	+0.431	+0.553	
Skeletal age at 9 years	-0.480		-0.423
Skeletal age at 11 years	-0.685		-0.637

	r	η	r	η	
Standing height increment 10 to 11 years	-0.627	0.688	-0.609	0.619	
Standing height increment 11 to 12 years	-0.043	0.663	-0.091	0.502	
Standing height increment 12 to 13 years	+0.648	0.776	+0.523	0.640	
Standing height increment 13 to 14 years	+0.764	0.820	+0.679	0.704	

COMPARATIVE CORRELATIONS BETWEEN MENARCHEAL AGE AND OTHER PHYSICAL MEASURES

Table XI shows some comparative correlations between chronologic age at menarche and standing height, weight, skeletal age and their annual increments. The Harvard Growth data are from Shuttleworth[9] and the Chicago Laboratory School data are from Flory.[5] Despite both numerical and qualitative differences in population samplings, correlations derived from Brush data are similar to those from the two other samplings at the ages when they are available for comparison. The rela-

tionships, it may be concluded, tend to be relatively constant and independent of sampling differences.

COMPARISON OF INDIVIDUAL CURVES OF STANDING HEIGHT, SKELETAL AGE, AND WEIGHT

Figs. 11 through 16 are graphical representations of standing height, skeletal age and weight of individual girls.

The two girls (No. 3513 and No. 3882) whose growth and development curves appear in Fig. 11 were chosen for comparison because their chronologic ages at menarche (150 months) and their interpolated skeletal ages at menarche (157 months) coincide. From 8 years through 15 years their skeletal age assessments are very similar; thus, they are

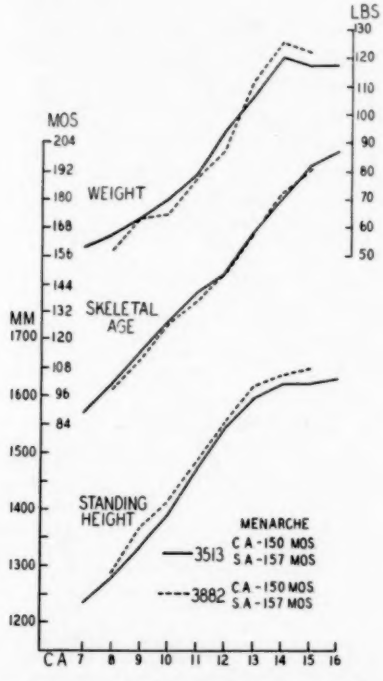

Fig. 11.—Standing height, weight, and skeletal age of two girls, No. 3513 and No. 3882.

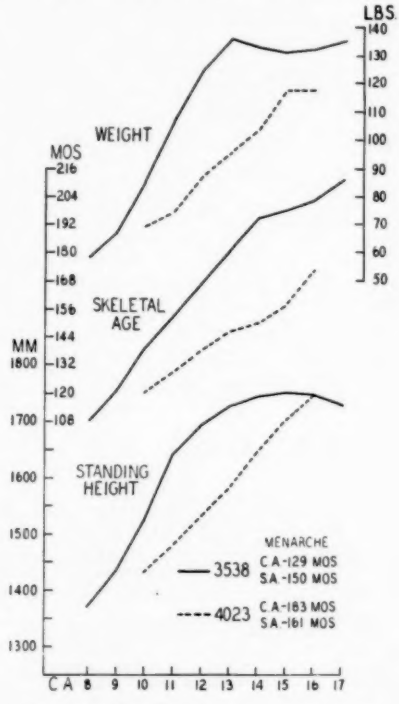

Fig. 12.—Standing height, weight, and skeletal age of two girls, No. 3538 and No. 4023.

maturing at the same rate and on the same level. Their standing heights maintain a close relationship to one another as do also their weights, which, however, show more marked irregularities. This suggests that the differences between the heights of two individuals and between the weights of two individuals tend to remain approximately constant as long as they maintain the same rate and level of skeletal maturation.

The two girls (No. 3538 and No. 4023) represented in Fig. 12 were chosen for comparison because of the large difference (54 months) in their chronologic ages at menarche; there is a difference of eleven months in their interpolated skeletal ages at menarche. The skeletal ages of these girls from 10 to 16 years are progressing at neither the same rate

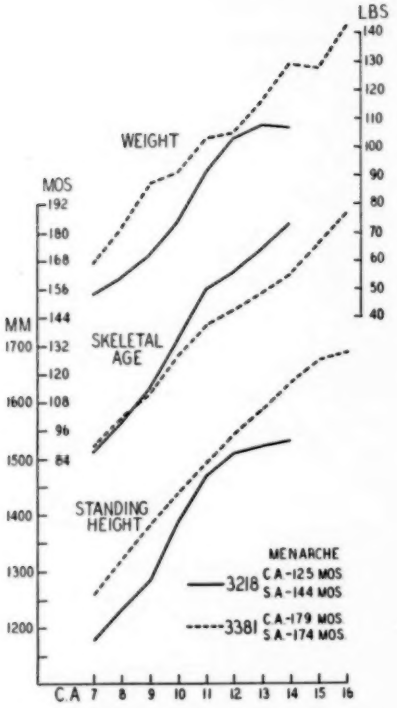

Fig. 13.—Standing height, weight, and skeletal age of two girls, No. 3218 and No. 3381.

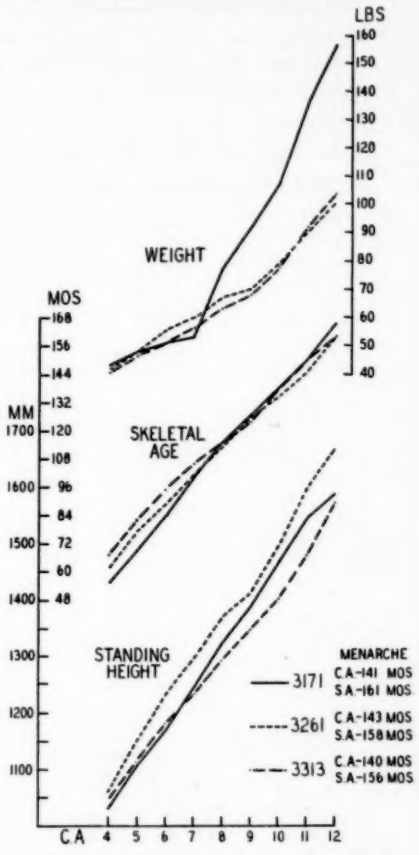

Fig. 14.—Standing height, weight, and skeletal age of three girls, No. 3171, No. 3261, and No. 3313.

nor on the same level. The girl with the early menarche and advanced skeletal age has a short, intensive, premenarcheal spurt in height; the girl with the late menarche experiences a long period of regular growth with a scarcely appreciable acceleration in increment near the menarche. By the age of 15 years the advanced girl has attained her adult stature; the retarded girl is still growing at a steady rate and by the age of 16 years her height equals that of the early maturing girl. She will have a terminal height greater than that of the girl with the early menarche, although at the age of 11 years her height was 160 mm. less. At the age

of 16 years one girl (No. 4023) is still retarded relative to the other (No. 3538) in both weight and skeletal age.

The two girls (No. 3218 and No. 3381) represented in Fig. 13 are characterized, respectively, by the lowest and highest interpolated skeletal ages at the menarche. There is a difference of fifty-four months between their chronologic ages at the menarche (one girl, No. 3218, having the lowest menarcheal age also of our series) and a difference of thirty months between their interpolated skeletal ages at the menarche. They thus represent the two extremes of the skeletal age-at-menarche distribu-

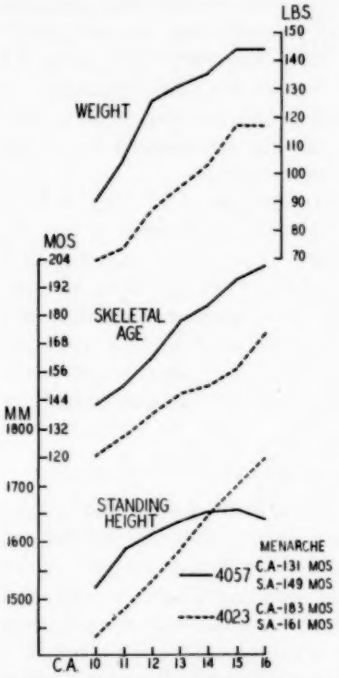

Fig. 15.—Standing height, weight, and skeletal age of two girls, No. 4057 and No. 4023.

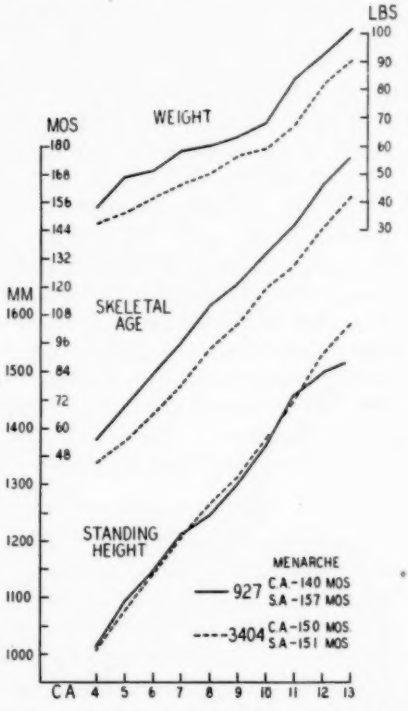

Fig. 16.—Standing height, weight, and skeletal age of two girls, No. 927 and No. 3404.

tion, or the worst examples in our series of the skeletal age-menarcheal age association. The skeletal age curve of one (No. 3218) is atypical in its acceleration between 9 and 11 years of age from average ratings at 7 and 8 years. This acceleration in skeletal development is coincident with accelerations in height and weight. The difference between these two girls' menarcheal ages could not have been predicted from their skeletal age assessments at 7, 8, or 9 years of age.

Height, weight, and skeletal age curves of three girls (No. 3171, No. 3261, and No. 3313) whose chronologic ages at the menarche are 141, 143, and 140 months, respectively, appear in Fig. 14. There is nothing

in the health history of the one girl (No. 3171) to explain her decelerating weight increments from 4 to 7 years of age; thereafter there is a history of overeating. This illustrates the inadequacy of weight as an indicator of maturational level, even though in groups early menarcheal age tends to be associated with greater than average weight and with a greater than average weight-height index at the premenarcheal years.

Shown in Fig. 15 are the standing height, skeletal age, and weight curves of two girls (No. 4057 and No. 4023) for the ages 10 to 16 years; their chronologic ages at menarche differ by fifty-two months, their interpolated skeletal ages at menarche differ by twelve months. One (No. 4057) is advanced over the other (No. 4023) in all three measures at the age of 10 years, but by the age of 16 years the relative positions of the two girls in standing height are reversed. The girl who is advanced in skeletal maturation and in weight has reached her adult height by the age of 14 years, whereas the retarded girl is still growing at an almost constant rate at the age of 16 years, having experienced but little acceleration in height increment before her menarche.

The two girls (No. 927 and No. 3404) represented in Fig. 16 have strikingly similar standing heights from 4 years to 11 years of age, although throughout this period one (No. 927) is advanced over the other (No. 3404) in both skeletal age and weight. The girl who is more retarded in skeletal age and in weight will have a greater terminal height than the other girl. The difference in their terminal heights could not have been predicted from their heights or from their height increments before the age of 13 years. The girl whose skeletal age and weight are advanced has the earlier menarche.

FAMILIAL LIKENESSES IN GROWTH AND DEVELOPMENT

Two of the Brush Regular Series girls (No. 3218 and No. 3381) have been described in the preceding section as the girls with skeletal age ratings at the menarche which are the lowest and highest respectively of our series. Presented in Fig. 17 are the standing height, weight, and skeletal age curves of Elizabeth (No. 3218) (menarcheal age 10 years, 5 months; interpolated skeletal age at menarche, 12 years) together with those of her two siblings, a sister Nancy (No. 3113) and a brother Richard (No. 3059). Elizabeth's examinations range from 4½ years to 14 years of age; Nancy's examinations began at the age of 3 months and have continued through 10 years; Richard had his first examination at 3 years of age and his last (1941) examination at the age of 13. Nancy, like Elizabeth, has undergone a marked increase in rate of growth and development before the age of 10 years; Richard has experienced his prepuberal spurt in growth and development before the age of 12 years.

In contrast to these three siblings whose growth and development curves demonstrate a familial pattern of early maturation are Carolyn (No. 3381) (menarcheal age 14 years, 11 months; interpolated skeletal

age at menarche, 14 years, 6 months) and her brother Frederick (No. 3380), whose standing height, weight, and skeletal age curves appear in Fig. 18. Both Carolyn, with examinations from 7 years through 16 years of age, and Frederick, with examinations from 6 years through 15 years

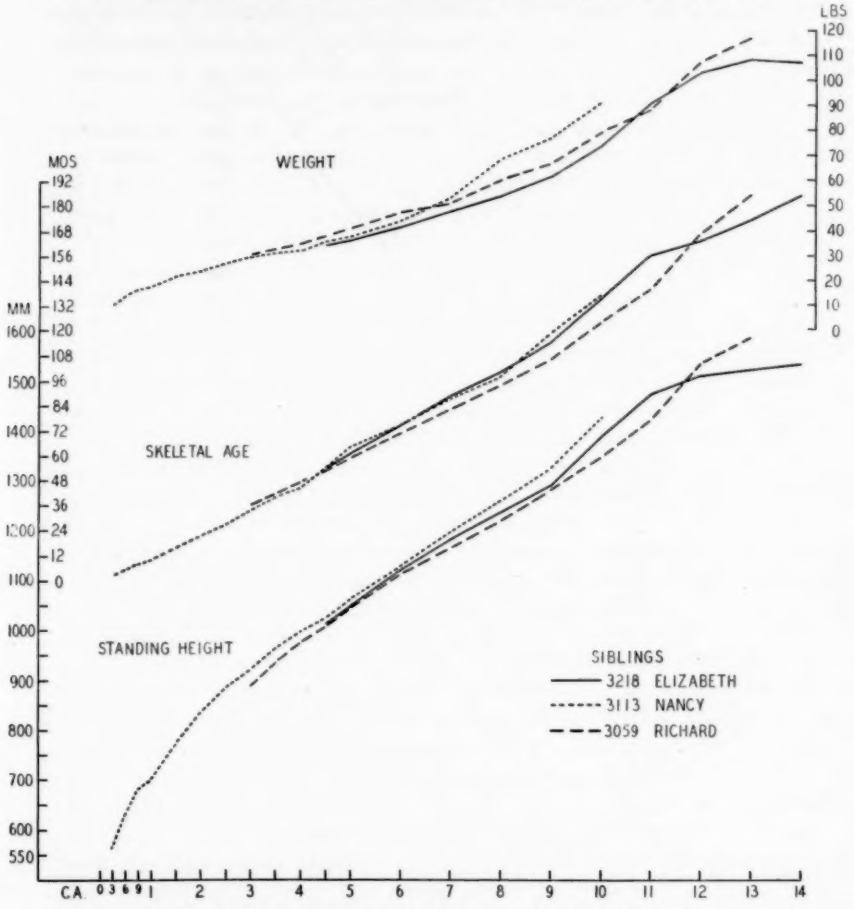

Fig. 17.—Standing height, weight and skeletal age of three siblings, No. 3218, No. 3113, and No. 3059.

of age, have had a growing period prolonged to more than the average extent over the adolescent years; their annual increments in standing height are quantitatively similar from year to year for a long period of years and they evidence little prepuberal acceleration in growth and development.

No indications of abnormality having appeared in these children's health histories, it may be concluded that it is "normal" for these two groups of siblings to deviate in opposite directions from the "norm" or

central tendency to a considerable extent and from each other to a great extent, both in absolute dimensions and in rate of development. Neither group of siblings is typical of our entire series of children; both may be considered characteristic of two relatively small classifications of the entire series; namely, the advanced, or early maturing children, and the retarded, or late maturing children. It is perhaps inadvisable to de-

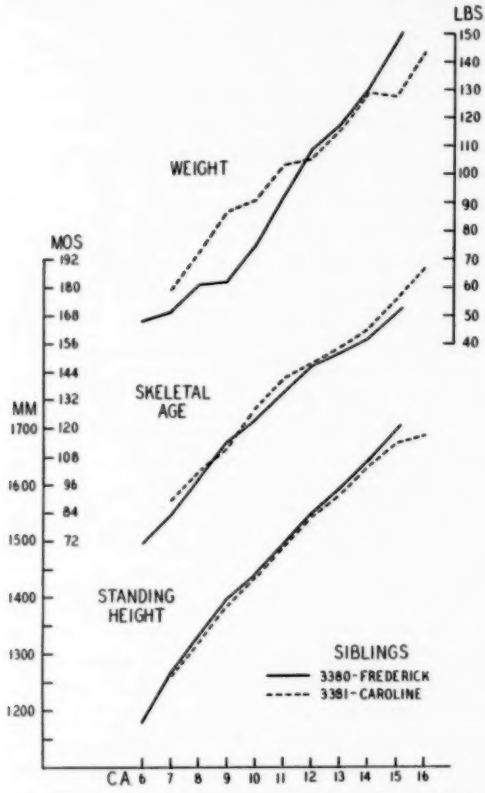

Fig. 18.—Standing height, weight, and skeletal age of two siblings, No. 3381 and No. 3380.

scribe these two classes of children as advanced and retarded since these words commonly carry a connotation of superiority in the one case and deficiency in the other case.

The tendency of siblings to follow growth patterns similar to one another was found by Boas among the siblings in his group of Hebrew Orphan Asylum children. He concluded:[4] ". . . it appeared that the brothers and sisters of the tall ones, who include many of those with rapid tempo of development, will also have a rapid tempo, an early time for the maximum rate of growth, a rapid rate and an early termination

of growth, while the brothers and sisters of the short ones, who include many of those with sluggish tempo of development, have a slow rate of growth, of less intensity and of longer duration."

SUMMARY

This report is based on 1,339 birthday examinations of 200 Brush Foundation Regular Series girls from 7 to 17 years of age. The data used are menarcheal age; measurements of standing height and weight; skeletal age assessments made according to the Todd 1935 standards of six areas—hand, foot, elbow, knee, hip and shoulder; annual increments in height, weight, and skeletal age; weight-height index. Brush Regular Series children are, as a group, above average socio-economically.

From 7 to 15 years of age the means of standing height of girls with early menarches are invariably greater than those of girls with late menarches.

From 7 to 16 years of age the means of weight of girls with early menarches are invariably greater than those of girls with late menarches.

From 7 to 16 years of age girls with early menarches are, as a group, characterized by greater weight for height than girls with late menarches.

From 7 to 17 years of age the girls in the early menarcheal age group are advanced in mean skeletal age over the girls in the average menarcheal age group, and the latter, in turn, are advanced in mean skeletal age over those in the late menarcheal age group.

The year of maximum increment in standing height is related to menarcheal age; the greatest mean annual height increment occurs between 10 and 11 years for girls with menarches from 10 years to 11 years, 11 months; between 11 and 12 years for girls with menarches from 12 years to 12 years, 11 months; and between 12 and 13 years for girls with menarches from 13 years to 15 years, 3 months. Values of maximum annual increments are negatively related to menarcheal age; girls with early menarches experience the greatest acceleration, followed by the greatest deceleration; girls with late menarches experience the least acceleration followed by the least deceleration. The average girl experiences her greatest height increment during the year preceding the year of menarche; maximum increment does occur during the year of menarche; it does occur during the second year preceding menarche, and some girls with late menarches seem to experience little or no premenarcheal acceleration. Maximum increment in standing height, in this series, never occurs after the menarche.

For three menarcheal age groups, early, average, and late, mean maximum increments in weight tend to be spread over a two-year period. The values of maximum increments are negatively related to menarcheal age. The decline in weight increment following the maximum is less marked than the decline in height increment; it is most marked for those with early menarches (and largest maximum increments), least marked for those with late menarches (and smallest maximum increments).

Skeletal age is more highly correlated with menarcheal age than are standing height, weight, weight-height index, or annual increments in standing height. Girls of early, average, and late menarcheal age groups can be differentiated by their assessments of skeletal maturity in advance of the menarche and in advance of the premenarcheal acceleration in height and weight.

The mean menarcheal age of 187 girls for whom interpolated skeletal ages at the menarche are available is 151.52 months; the mean interpolated skeletal age at menarche of these girls is 156.99 months. Chronologic age at menarche is about twice as variable as skeletal age at menarche. Fifty per cent of the 187 skeletal ages at menarche fall between ± three months of the mean, 156.99 months.

It is normal for some children to grow and to develop toward maturity at a rapid rate with, consequently, an early attainment of terminal size; it is normal for some other children to grow and develop toward maturity at a slow rate with, consequently, a late attainment of terminal size. The rate of growth, in this series, has no reliable relationship to terminal size.

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A STUDY OF HUMORAL ANTIBODIES FOR STAPHYLOCOCCUS AUREUS IN INFANTS AND THEIR MOTHERS

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THE frequency and severity of staphylococcal infections in early infancy prompted our interest in a study of humoral antibodies for *Staphylococcus aureus* during this period of life. The antibodies selected for study were antitoxin and anticapsular agglutinin.

Staphylococcal antitoxin has been studied by Bryce and Burnet,[1] who found that the blood of newborn infants contains amounts equal to or greater than that of their mothers' blood and that a striking decrease in the infants' titers occurs during the first few months of life. Unfortunately, they did not express their values in terms of international units. Murray[2] has shown that the average antitoxin titer of fifty mothers was 0.75 international units, of their newborn infants, 0.78. He stated that there was little variation in titer in the groups studied. His findings parallel closely those obtained by other authors for normal adults. Since the importance of staphylococcal antitoxin in human infections has been emphasized by the observations of Parish and associates,[3] Dolman,[4] and Murray,[2] we included it in the present studies.

Lyons[5] reported the results of experiments from which he concludes that a great difference between saprophytic and pathogenic staphylococci is the ability of the latter to produce capsules while growing in blood. Virulent staphylococci have the power to reproduce capsules even after they have been phagocytosed, with resulting destruction of the leucocytes and liberation of encapsulated organisms capable of further invasion and destruction of the tissues. Saprophytic strains, on the other hand, lose their capsules in this environment and are easily phagocytosed by leucocytes. Lyons was able to produce the capsule by growing the organisms in vitro under special conditions, and he also obtained effective type-specific agglutinins in rabbits. He regards this antibody as being "the essential antibacterial antibody for the staphylococcus." It seemed desirable, therefore, to compare the amounts of antitoxic and anticapsular antibodies for *Staph. aureus* in the blood of infants and their mothers.

METHODS

The samples of serum were obtained from venous or cord blood. Each sample was inactivated in a water bath at 56° C. for thirty minutes before the tests were made.

From the Departments of Pediatrics and Bacteriology, University of Rochester School of Medicine and Dentistry and Strong Memorial and Rochester Municipal Hospitals.

Determination of Antitoxin.—The staphylococcal toxin was prepared by a method similar to that of Dolman.[6] We used a toxigenic strain of *Staph. aureus.** Douglas's broth was substituted for beef infusion broth with 1 per cent of peptone. Petri dishes containing semisolid Douglas's agar (0.3 per cent of agar) were inoculated with 0.25 ml. amounts of a young broth culture of the organism. These plates were then incubated at 37° C. for thirty-six hours, in an atmosphere containing 20 per cent of carbon dioxide.

After incubation, the whole agar culture was passed through cheese cloth and filter paper by gravity to remove gross particles and then centrifuged to throw down the organisms. The supernatant was filtered through a Seitz E.K. disk. To the sterile filtrate, merthiolate was added to make a final concentration of 1:8,000. This was our toxin. When tested with 1 ml. amounts of a 1 per cent suspension of thrice-washed rabbit corpuscles, its hemolytic titer was 1:512, but the titer gradually fell to 1:8 during the course of a year. In spite of this deterioration in toxicity, the filtrate proved to be a satisfactory toxin, dilutions with physiologic saline being so adjusted from time to time that the amount of toxin used in each titration remained constant. This amount was repeatedly checked against a standard staphylococcal antitoxin,† which was diluted with saline so that each milliliter contained one international unit of antitoxin, and was stored in a sealed flask at 4° C.

Following the method of Parish[3] for the titration of antitoxin, 0.5 ml. amounts of the sera to be tested were serially diluted with saline 1:2, 1:4, 1:8, *etc.*, in 10 mm. test tubes. For each test or series of tests, 0.5 ml. of the standard antitoxin was always treated in the same manner as the unknown sera. Staphylococcal toxin was added in 0.5 ml. amounts to each tube, and after thorough shaking the racks were placed in a water bath at 37° C. for fifteen minutes. One milliliter of a 1 per cent suspension of fresh, thrice-washed rabbit corpuscles was added to each tube, and the resulting mixtures of toxin, serum, and indicator (rabbit erythrocytes) were again shaken, returned to the water bath at 37° C. for an hour, and finally kept in an ice-box at 4° C. overnight. When the tests were read on the following day, the greatest dilution showing complete inhibition of hemolysis was regarded as the antitoxin titer of that serum. This titer could be expressed in terms of international units by comparison with the titration of the standard antitoxin; that is, if an unknown serum completely inhibited the hemolytic activity of the toxin as far as the sixth dilution tube (1:64), while the standard antitoxin did so only to the fifth tube (1:32), then the unknown serum contained twice the amount of antitoxin as the standard—2 I.U. per milliliter.

Determination of Staphylococcal Anticapsular Agglutinin.—The titer of anticapsular agglutinin in the human sera studied was determined by the slide agglutination method of Lyons.[5] A hemolytic, toxin-producing *Staph. aureus* isolated from a case of acute osteomyelitis was used.

A shallow layer of Douglas's broth containing 0.05 per cent of glucose was inoculated with a twelve-hour culture of the organism, using 0.1 ml. of inoculum for each 5 ml. of broth. After three hours' growth at 37° C., the organisms were killed by slowly heating them to 100° C., centrifuged, and resuspended in saline to one-twentieth of the original volume. The serum to be tested was diluted with saline in the following manner: 1:10, 1:20, 1:40, *etc.*

One drop of the suspension of staphylococci was mixed with one loopful of the serum dilution on a clean glass slide. A control test of the organisms and saline was always made on the same slide. The test mixtures were gently rotated for five minutes and then read. The photographic charts published by Pauli and Coburn[7] served as standards for determining the degree of agglutination. For the sake of

*Kindly supplied by Dr. C. M. Carpenter.

†Obtained from the Lederle Laboratories, Inc., New York, N. Y.

uniformity, the greatest dilution of a serum that resulted in a 4 plus agglutination was considered to be the titer of that particular serum.

The difficulty of obtaining venous blood from infants led us to devise a method requiring only the small amount of serum readily obtainable from capillary blood. The details and accuracy of titrating the antitoxin and anticapsular agglutinin of *Staph. aureus* by this method are described elsewhere.[8] The method proved to be quite satisfactory and was used for the determination of some of the values reported in the present study.

RESULTS

The results are presented in Tables I to V and Figs. 1 to 5. Fig. 1 shows the correlation between the serum antitoxin of mothers and newborn infants. Each dot represents the titer of a mother and her offspring. It is quite obvious that the correlation is of a high degree because the dots fall in an almost straight line and the regression lines are nearly superimposed. This correlation was previously observed by Bryce and Burnet[1] and by Murray.[2] The average value for each group, together with standard deviation, coefficient of correlation, and probable error of the same are presented in Table I.

TABLE I

CORRELATION OF ANTITOXIN IN THE SERA OF FIFTY MOTHERS AND THEIR NEWBORN INFANTS

	NUMBER	MEAN	STANDARD DEVIATION	r	P.E. OF r
Mothers	50	0.502 u	±0.405	0.900	0.018
Newborns	50	0.737 u	±0.611		

u = International unit of staphylococcal antitoxin per milliliter of serum.
r = Coefficient of correlation.
P.E. = Probable error.

TABLE II

CORRELATION OF ANTICAPSULAR AGGLUTININS IN THE SERA OF FIFTY MOTHERS AND THEIR NEWBORN INFANTS

	NUMBER	MEAN	STANDARD DEVIATION	r	P.E. OF r
Mothers	50	8.8 u¹*	5.185	0.539	0.0675
Newborns	50	7.32 u¹	4.945		

*u¹ = Arbitrary unit of agglutinins per milliliter of serum.
2 units = 1:160 dilution of subject's serum.
4 units = 1:320 dilution of subject's serum.
8 units = 1:640 dilution of subject's serum.
16 units = 1:1280 dilution of subject's serum.

Fig. 2 represents the same type of correlation graph for the serum agglutinins of mothers and newborn infants. In this case one finds a fairly wide scatter of the dots, and the angle formed by the regression lines is less acute. The average values are presented in Table II, and for the sake of convenience the serum dilutions are represented by arbitrary units. The coefficient of correlation is not so high as that for the antitoxin titers, but since it is eight times its probable error, it shows

a statistically significant degree of correlation between the agglutinin titer of mother and newborn infant.

In order to demonstrate any possible correlation between the titers of the two antibodies studied, Fig. 3 has been arranged so that each dot represents the titers of both antibodies in a mother's serum, and each

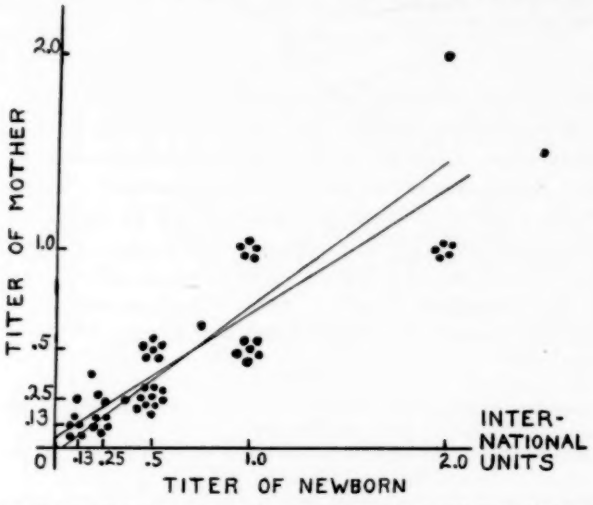

Fig. 1.—Correlation of staphylococcal antitoxin in mothers and their newborn infants.

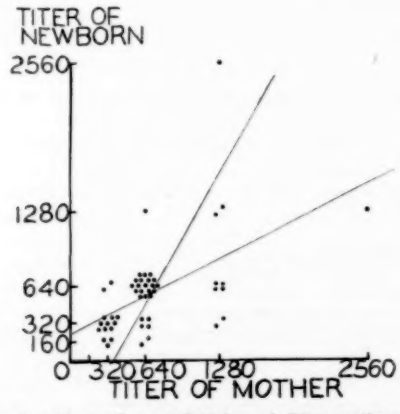

Fig. 2.—Correlation of anticapsular agglutinins of fifty mothers and their newborn infants.

circle represents similar values for a newborn infant's serum. It is possible to use 100 sera, because in this instance one is not interested in a correlation between mother and offspring, but rather between two different types of staphylococcal antibody. The very wide scatter of both

dots and circles is quite apparent, and the regression lines are almost at right angles to each other. The average values are shown in Table III, where again the agglutinin titer is expressed in terms of units. The coefficient of correlation is quite low and not statistically significant. In other words, the results show that in the 100 sera studied, the two antibodies varied independently of each other.

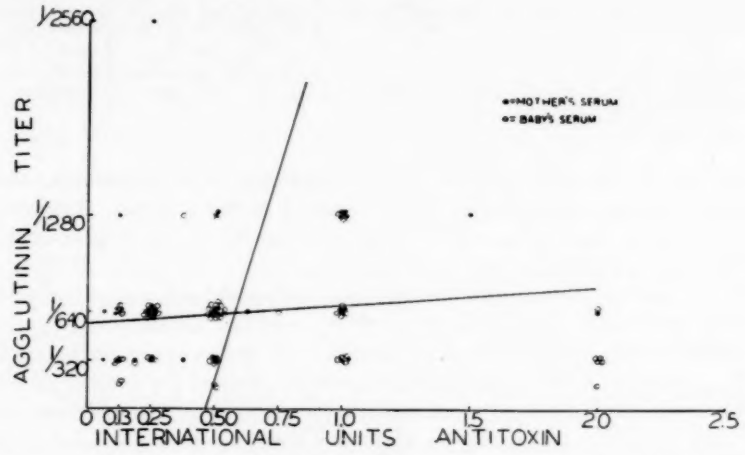

Fig. 3.—Correlation of anticapsular agglutinin and antitoxin for *Staphylococcus aureus* in 100 sera.

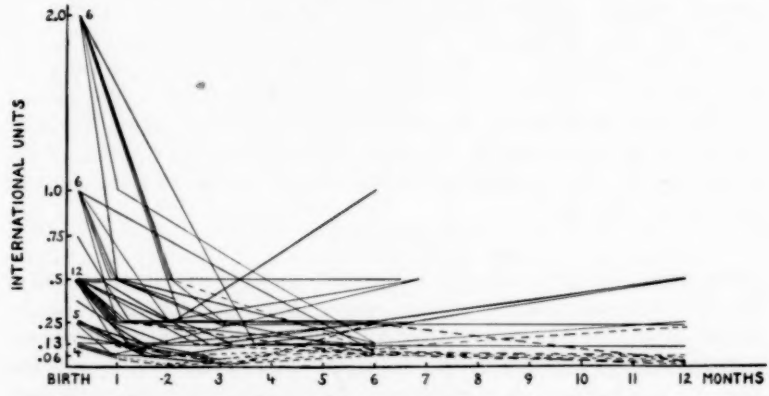

Fig. 4.—Determination of staphylococcal antitoxin in "normal" human sera during the first year of life; 0.74 units = average titer for fifty newborn infants, 0.5 units = average titer for their mothers.

It was possible to follow only a part of the fifty newborn infants during the first year of life. Fig. 4 shows the titer of antitoxin at several age periods. In this chart, each line connects the values for a single infant. There is a striking and almost universal decrease in titer during

the first few months. It is particularly interesting to note that the higher the titer at birth, the more pronounced the fall during the early weeks of life. In most of the infants a gradual downhill trend was observed or the level remained about the same during the first year of life. In a few there was a slight increase. The baby showing the striking

TABLE III

CORRELATION OF ANTITOXIN AND ANTICAPSULAR AGGLUTININ IN 100 HUMAN SERA

	NUMBER	MEAN	STANDARD DEVIATION	r	P.E. OF r
Antitoxin	100	0.6196 u	0.531	0.1796	0.0653
Anticapsular agglutinin	100	8.06 u[1]	5.126		

rise at an age of 6 months was convalescing from pneumonia, and *Staph. aureus* was the only pathogen isolated from his throat. The term "normal" is used in the title of Fig. 4 because by the latter part of the first year of life almost all of the infants had had infections of the upper respiratory tract. The broken lines connect known values for antitoxin titer with those so low that they could not be measured by the method used. The actual values and their averages are given in Table IV. Perhaps it is not justifiable to present averages for the 6- and 12-month age levels because so many of the values were too low to determine.

Fig. 5 represents the agglutinin titers determined on the same blood samples from which the antitoxin values were obtained. Here again each line represents the various observations for a single infant. In striking contrast to the antitoxin, one finds little if any reduction in agglutinin titer during the entire twelve months. The actual values for this chart are given in Table V. One might conclude from the averages that there had been a striking decrease in agglutinin titer during the period of observation, but one must bear in mind that the range of 320 to 640 is represented by a single tube in the serial dilution of the serum tested. The number of horizontal lines in Fig. 5 is in contrast with that of Fig. 4.

DISCUSSION

The high degree of correlation found between the antitoxin titers of the mothers and their newborn infants indicated the probable dependence of the newborn's titer on that of the mother. However, a comparison of the titers of the fifty pairs measured revealed a greater titer for the newborn in thirty cases. In eighteen pairs, the titers were identical, and in only two of the infants was the titer less than that of the mothers. This finding of a greater concentration of staphylococcal antitoxin on the infant's side of the placenta has been observed before by Bryce and Burnet.[2]

The degree of correlation between the anticapsular agglutinin titers of the fifty pairs, although positive and statistically significant, was much

TABLE IV

INTERNATIONAL UNITS OF STAPHYLOCOCCAL ANTITOXIN PER MILLILITER OF SERUM DURING THE FIRST YEAR OF LIFE

PATIENT	BIRTH	1 TO 3 MONTHS	5 TO 7 MONTHS	1 YEAR
Ang.	0.50	0.13		
Par.	0.50	0.25		
T. Ha.	1.00	0.25		
Off.	2.00	0.13		
Con.	0.13	0.06		
Lane	0.38	0.06		
Oliv.	0.75	0.25		
Wag.	0.13	0.13		
Amm.	0.25	0.13		
Warr.	1.00	0.50		
Naw.	1.00		<0.13	
Cres.	0.50		0.50	
Pal.	2.00	1.00	0.13	
Sac.	0.50	0.25	0.25	
Ros.	0.50	0.13	0.25	
Bates	2.00	0.13	0.13	
Tor.	2.00	0.50	0.13	
Bouch.	0.13	0.06	0.13	
Im.	0.25	0.06	<0.13	
Pasc.	0.50	0.25	1.00*	
Pender	1.00	0.25	0.25	
Mirag.	0.50	0.06	0.25	
Fin.	0.25	0.06	0.50	
Dau.	1.00	0.25	0.50	
Min.	0.50	<0.06		0.25
Houl.	0.50	0.13		0.50
Marr.	1.00	0.25		0.25
McC.	0.50	0.13		0.13
Ses.	0.13	<0.06	0.13	0.25
Moor.	0.25	0.06	0.25	0.50
Batt.	0.50	0.13	<0.13	<0.06
Gr.	0.25	0.03	<0.13	<0.06
Lib.	2.00	0.50	0.13	<0.06
Chr.	2.00	0.50	<0.13	<0.06
Barr.	0.50	0.13	0.25	<0.06
Tud.	0.50	0.25	<0.13	0.06
Average units of antitoxin	0.76	<0.21	<0.25	<0.19
Number	36	34	22	12

*Baby convalescent from pneumonia.

less than that for the antitoxin titers. Unlike the antitoxin values, the agglutinin titers of thirty pairs were identical, in sixteen pairs the mother had a greater titer, in four pairs the newborn infants. The larger intervals of dilution in the quantitative measurement of the agglutinin content of the sera probably accounted for poorer correlation as compared to the antitoxin titers. The use of carefully standardized antigens and smaller intervals of dilution of the sera might have improved the correlation, but this was impractical.

Practically no correlation was found between the titers of the two antibodies in the 100 sera tested. The greater spread of the antitoxin values would suggest that natural contact of individuals with staphylococcal toxin was more variable than with bacterial cells. The probability of a variable response in each individual to the two antigenic sub-

TABLE V

TITER OF ANTICAPSULAR AGGLUTININS DURING THE FIRST YEAR OF LIFE

PATIENT	BIRTH	1 TO 3 MONTHS	5 TO 7 MONTHS	1 YEAR
Oliv.	640	320		
Pasc.	1280	640		
Par.	160	160		
Fin.	640	640		
La.	640	640		
Amn.	640	640		
Off.	320	160		
T. Ha.	320	320		
Bouc.	640		320	
Pen.	640		160	
Pal.	640		640	
Cris.	640		320	
Tov.	320	320	320	
Min.	640	320	320	
War.	640	640	320	
M. Co.	640	320		640
Tud.	160	320		320
Cou.	160	320		160
Dau.	320	320		320
Mir.	640	640		320
Sac.	640		320	320
Mar.	640	640	640	640
Ros.	320	320	320	640
Gri.	640	320	320	320
Lib.	320	320	320	320
Chr.	320	320	160	160
Hou.	640	160	320	320
Bar.	640	160	640	320
Ses.	320	320	640	640
Moo.	640	640	320	640
Im.	320	320	320	320
Bat.	640	320	160	320
Bat.	160	320	320	320
Average	514	389	360	391
Number	33	28	20	18

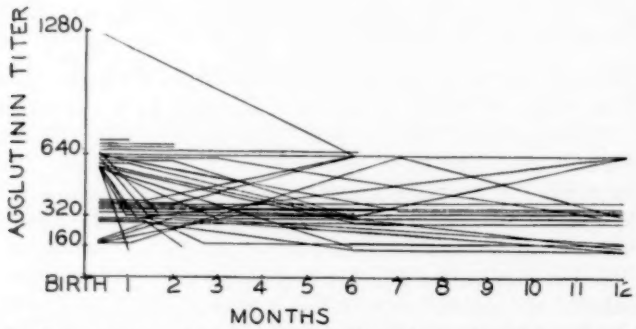

Fig. 5.—Determination of staphylococcal anticapsular agglutinin in normal human sera during the first year of life; 585 = average titer for newborn infants; 704 = average titer for their mothers.

stances appears less tenable. Many other unknown factors may account for the lack of correlation between the two antibodies. Our results differ from those of Neill and co-workers,[9-11] who studied diphtheric agglutinin and antitoxin titers in normal sera. They found that by comparing the average for a group of adults, a high agglutinin titer was associated with a high antitoxin content of the serum. For some of the individuals comprising this group, however, there was much less agreement between the two antibodies. They did not submit their values to statistical analysis, and their sample for study was not chosen at random, as in the present series. Hence, it is difficult to compare their results with ours.

The antibodies transferred from mother to newborn infant may be expected to disappear within a comparatively short time. Despite an initial range of from 0.13 to 2.0 units of antitoxin, each infant observed reached a low level within four months after birth and tended to remain at that level until 1 year of age. Our results agree with the average results obtained by Bryce and Burnet[2] in a similar study.

We are unable to explain why the infants with a relatively high titer at birth showed a more precipitous decline than those with low titers. The results are in agreement with those of Buchman,[12] who studied adult patients with osteomyelitis. He noted that when staphylococcal antitoxin was increased by injections of toxoid, the individual with a higher titer showed the same rapid decline after active immunization was discontinued.

The agglutinin titer behaved quite differently during the first year of life, remaining practically at a constant level. The maintenance of the initial titer during this period did not seem to depend upon breast feeding, because most of the infants received little or no breast milk. The role of infection could be ruled out by the absence of clinical staphylococcal infections, except in one infant. The universal presence of staphylococci on the skin and in the nose and throat, and possibly their ingestion, may provide an adequate stimulus to agglutinin production without concomitant antitoxin formation. In a single newborn infant Neill and associates[10] found a rapid drop of diphtheric antitoxin and agglutinin in the first five months of life, without subsequent rise in titer up to 12 months of age. They suggested that no active immunity developed during this time because no virulent diphtheria bacilli were present in the baby's environment.

Since no outbreaks of staphylococcal infections occurred in the nurseries during the present study, it was impossible to obtain direct evidence of the relative importance of the two antibodies in staphylococcal infections. Recently Cass,[13] in her discussion of the problem of clinical staphylococcal infections of the newborn infant, stated, "It appears that although the *Staph. aureus* is constantly present in the surroundings

of the newborn, it is pathogenic to only a few." During this period of life, the role of staphylococcal antibodies as a possible protective mechanism requires further study.

The term "anticapsular agglutinin" was suggested by Lyons. Although we followed Lyons's technique in detail, we were unable to demonstrate the presence of a capsule around the staphylococci. Spink[14] has experienced the same difficulty. It was felt advisable, nevertheless, to use Lyons's term. The "anticapsular agglutinin" may well be the antibody for a surface antigen.

CONCLUSIONS

The blood of fifty pairs of mother and newborn was studied for its content of antitoxin and anticapsular agglutinin for *Staph. aureus.*

The results indicate that for each of the two antibodies studied, the newborn reflects its mother, with a higher degree of correlation for the antitoxin than for the agglutinin.

The titers of the two antibodies varied quite independently in the blood of 100 individuals.

In general the level of antitoxin showed a sharp decrease during the first few months of life, while the agglutinin titer remained practically unchanged throughout the first year.

A micromethod for the simultaneous determination of both types of antibody proved helpful.

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DISTURBED KIDNEY FUNCTION IN THE NEWBORN INFANT ASSOCIATED WITH DECREASED CALCIUM: PHOSPHORUS RATIO

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RECENTLY in the investigation of cases of what was believed to be tetany of the newborn infant, we have found, in addition to the disturbance of blood serum calcium, an associated retention of nitrogen and phosphorus. By following this form of investigation in all cases, it has been found that a large number of these supposed cases of tetany of the newborn infant are probably a result of lack of renal function. In a large number the symptoms are relieved by fluid and calcium gluconate given intravenously.

Case 1.—Baby M., admitted at 11 days of age, weighed 6 pounds, 15¾ ounces at birth and was delivered with low forceps; resuscitation was difficult. The baby seemed normal for one week, then began to lose weight and breathe rapidly. The condition was diagnosed as pneumonia by the family doctor. The infant was breathing rapidly, had no chest signs, and was somewhat cyanosed. There was some twitching of hands. On January 7 blood serum* showed calcium, 10.4 mg. per cent; phosphorus, 11.0. January 9—nonprotein nitrogen, 132; creatinine, 3.7. Two days later—calcium, 9.9; phosphorus, 7.8. January 14 (one week later)—calcium, 10.0; phosphorus, 8.0; nonprotein nitrogen, 57; creatinine, 3.15. January 22—calcium, 6.8; phosphorus, 10.6; nonprotein nitrogen, 78; creatinine, 3.48. February 5—nonprotein nitrogen, 120; creatinine, 3.49. Urine from admission to death showed albumin 1 to 2 plus, red cells, occasional granular casts, and pus. The infant was given continuous intravenous administration of glucose in saline and calcium gluconate, 10 c.c. of 10 per cent solution, was repeated in twelve hours. The infant improved and seemed quite well. Intravenous administration would be stopped for a few days and then symptoms of rapid breathing and convulsions would recur. After restarting intravenous administration and giving calcium gluconate, the symptoms would disappear. Eventually after one month, all available veins were used up and the child died. Post-mortem showed bilateral congenital hypoplasia of kidneys.

Case 2.—Baby G., admitted at 6 weeks of age, had a birth weight of 8 pounds, 4 ounces, and was breast fed for two weeks, then given evaporated milk, water, and corn syrup. No cod-liver oil was given. Six hours before admission the baby had an attack in which he held his breath and became very white in the face. He was dehydrated and appeared moribund on admission. Blood calcium, 9.2; phosphorus, 6.5; nonprotein nitrogen, 66; creatinine, 1.5. Urine showed albumin and a few pus cells. The baby was given intravenous administration of glucose and saline, blood

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*Normal estimations:
Serum calcium, 9.5 to 11 mg. per cent. (Kramer-Tisdall method, J.B.C. 47: 475, 1921.)
Serum phosphorus, 4.5 to 6 mg. per cent. (Fiske and Subbarow, J.B.C. 66: 375, 1925.)
Nonprotein nitrogen of blood, 25 to 35 mg. per cent. (Folin-Wu, J.B.C. 38: 81, 1919.)
Creatinine of blood, 1 to 2 mg. per cent. (Folin-Wu, J.B.C. 38: 81, 1919.)

transfusion, and 10 c.c. of calcium gluconate intravenously, as well as daily administration of calcium chloride by mouth, 15 gr. every four hours, and 15 minims of percomorphum liver oil. The infant developed bronchopneumonia and died five days after admission. Post-mortem examination showed bronchopneumonia, absence of right kidney, hypertrophy of left kidney and hydroureter, with obstruction at ureterovesical orifice.

CASE 3.—Baby H. was admitted at 2 days of age, weighing at birth 8 pounds, 4 ounces. There was a history of extremely difficult labor, fifty hours, with high forceps used. The obstetrician did not expect to obtain a living child. There was marked difficulty in resuscitation; the baby was drowsy since birth and had a twitching body and face. Carpopedal spasm was present intermittently. Blood calcium, 7.9; phosphorus, 6.6; nonprotein nitrogen, 59; creatinine, 1.8. The infant was given intravenous administration of glucose and saline and calcium gluconate, 10 c.c. of 10 per cent solution, every twelve hours for three doses and made an uninterrupted recovery. Blood calcium two days later, 11.6; phosphorus, 13.0; nonprotein nitrogen, 41; creatinine, 1.3. One week after admission the calcium was 9.4; phosphorus, 5.7; nonprotein nitrogen, 22; creatinine, 1.0. The infant continued well at 1 year of age. Urine contained a trace of albumin and an occasional cast.

CASE 4.—Baby C. was admitted at 3 days of age, with a birth weight of 6 pounds, 12 ounces. Labor was difficult, forceps used; resuscitation was difficult. The infant was twitching for two days, and the temperature had elevated to 106° for one day; and anuria was present from birth. The baby had a high-pitched cry. On examination the fontanel was full and sutures separated. Extremities were spastic and the infant was convulsing. Lumbar puncture showed blood-tinged spinal fluid with xanthochromia. Blood calcium was 7.6 mg. per cent; phosphorus, 10.1; nonprotein nitrogen, 160; creatinine, 7.6. The infant was given continuous intravenous administration of glucose and saline and calcium gluconate, 10 c.c. of 10 per cent solution, every twelve hours for four doses. The twitching stopped and the condition improved generally but the infant did not void until five days after admission, at which time he was 8 days old. Repeated attempts at catheterization were unsuccessful, and intravenous pyelogram was done in order to determine whether there was any renal apparatus. No dye was observed up to two and one-half hours after injection. However, the following day the baby voided and has ever since. Two days before voiding blood calcium was 9.8; phosphorus, 5.6; nonprotein nitrogen, 145; creatinine, 10.2. Two days after the baby voided, calcium was 9.8; phosphorus, 3.0; nonprotein nitrogen, 115; creatinine, 6.55. One week after voiding, nonprotein nitrogen was 65; creatinine, 1.8. Two weeks after voiding, nonprotein nitrogen was 47; creatinine, 1; calcium, 10.3; and phosphorus, 6.2. The urine showed albumin 2 plus and a number of red blood cells, white blood cells, and casts on first specimen but has been normal microscopically since. When intravenous administration was stopped after seventy-two hours, hypodermoclyses were given; the child appears to be making good recovery.

CASE 5.—Baby N., admitted at 1 day of age, with birth weight of 7 pounds, 7 ounces, was sent to the hospital because of twitching of the limbs. Examination showed a newborn baby convulsing and with a positive Chvostek's sign; also there was a slight icterus. Blood calcium was 10.7; phosphorus, 8.7; nonprotein nitrogen, 63. April 27—calcium, 9.7; phosphorus, 7.6. One week later the calcium was 11.1; phosphorus, 5.8; nonprotein nitrogen, 26; creatinine, 1.25. The urine showed a trace of albumin. The infant was given intravenous administration of glucose in normal saline and 10 c.c. calcium gluconate on three occasions during the first twenty-four hours and has made an uninterrupted recovery.

CASE 6.—Baby M., 1 day of age, weighing 6 pounds, was born by difficult breech extraction and was resuscitated with difficulty. The mother had a moderately se-

vere toxemia. The infant was vomiting and breathing poorly. Physical examination revealed some atelectasis. Blood serum calcium was 8.0 mg. per cent; phosphorus, 8.1; nonprotein nitrogen, 82; creatinine, 3.1. The infant was treated with intravenous administration of glucose in saline, and 10 c.c. of 10 per cent calcium gluconate solution were given intravenously on three occasions. The vomiting and respiratory difficulty cleared, and the child made an uninterrupted recovery. Three days after admission the calcium was 9.9 mg. per cent; phosphorus, 5.6; nonprotein nitrogen, 46; creatinine, 1.55; ten days after admission the laboratory findings showed calcium, 10.0; phosphorus, 6.7; nonprotein nitrogen, 30; creatinine, 0.90. The urine contained a trace of albumin for the first week the infant was in hospital.

CASE 7.—Baby H., 4 weeks of age, with birth weight of 7 pounds, 14 ounces, was delivered by forceps with no difficulty in resuscitation. The infant began having difficulty in breathing and vomiting two days before admission. The child was cyanosed the afternoon of admission. The family doctor diagnosed an obstruction, of some type, to the baby's breathing. The baby was breast fed; no cod-liver oil or orange juice was given. The infant was cyanosed and because of poor air entry the cyanosis was thought to be due to a possible foreign body in the lung. An x-ray showed the heart to be quite enlarged. Blood serum calcium was 7.3 mg. per cent; phosphorus, 7.4; nonprotein nitrogen, 43; creatinine, 1.22; serum protein, 4.38 Gm. per cent. The baby was given intravenous administration of glucose and saline with 10 c.c. of 10 per cent calcium gluconate solution. There was some improvement in symptoms. The calcium gluconate was repeated two days later. The baby seemed to be doing well but had some bronchopneumonia and cardiac enlargement. Blood calcium was 9.0; phosphorus, 4.0 mg. per cent. Ten days after admission the baby was doing well, suddenly became cyanosed, and began to breathe rapidly. Nonprotein nitrogen was 76 mg. per cent; creatinine, 1.3. The baby died shortly after this test. Urine showed a trace of albumin during the stay in hospital. Post-mortem examination revealed a coarctation of the aorta and bronchopneumonia.

CASE 8.—Baby P., 1 day of age, with birth weight of 4 pounds, was delivered by cesarean section. The mother was extremely ill with eclampsia and convulsions. The infant started to twitch in the afternoon four hours before admission. There were twitching of arms and legs and intermittent tendency to carpopedal spasm. Blood calcium was 7.9; phosphorus, 5.7; nonprotein nitrogen, 74; creatinine, 3.8. The infant was given continuous intravenous administration of glucose and saline and 10 c.c. of calcium gluconate every twelve hours for three doses. One week after admission blood calcium was 8.7; phosphorus, 4.9; nonprotein nitrogen, 34. One month later, blood calcium was 12.7; phosphorus, 6.0; nonprotein nitrogen, 20; creatinine, 0.78. The urine showed albumin trace, throughout, and a few pus cells for the first two weeks. The infant is progressing satisfactorily and has been receiving 20 drops of percomorphum liver oil since 1 week of age.

CASE 9.—Baby M., 5 days of age, with birth weight of 6 pounds, had difficulty in breathing since birth and had blue spells starting one day before admission. Labor was normal and resuscitation not difficult. On admission the baby was jaundiced, breathing rapidly, with numerous fine râles throughout chest. Blood calcium was 7.6; phosphorus, 5.5; nonprotein nitrogen, 40; creatinine, 1.75; urine showed albumin 3 plus, occasional red blood cells. The infant was given intravenous administration of glucose and saline and 10 c.c. of calcium gluconate every twelve hours for two doses. Symptoms disappeared and the infant has made recovery. One week after admission the blood calcium was 10.0; phosphorus, 4.8; nonprotein nitrogen, 44; creatinine, 1.6. Further tests ten days after admission showed nonprotein nitrogen to be 32; creatinine, 1.3.

TABLE I

CASE	SYMPTOMS	AGE (DAYS)	CAL.	PHOS.	N.P.N.	CREAT.	REMARKS
1	Difficult delivery and resuscitation; rapid breathing, blue spells	11 25	10.4 6.8	11.0 10.6	132 78	3.7 3.48	I.V. glucose and saline + calcium gluconate; improved temporarily; died—hypoplastic kidneys
2	Dyspnea, pallor, breath-holding spell	40	9.2	6.5	66	1.5	I.V. glucose and saline + calcium gluconate; improved temporarily; died—single kidney with hydronephrosis
3	Difficult delivery and resuscitation; blue spells, twitching, carpopedal spasm, high-pitched cry	2 4 10	7.9 11.6 9.4	6.6 13.0 5.7	59 41 22	1.8 1.3 1.0	I.V. glucose and saline + calcium gluconate—symptoms promptly relieved; child well at 3 months of age
4	Difficult delivery and resuscitation; twitching of face and mouth; attacks of cyanosis; anuria since birth; temp., 106°	3 6 10 15	7.6 9.8 9.2	10.1 5.6 3.0	166 145 115 65	7.6 10.2 6.5 1.8	I.V. glucose and saline + calcium gluconate; voided at eight days of age; has improved since and seems normal now
5	Twitching, convulsions, Chvostek's sign; mother had toxemia	1 9	10.7 11.1	8.7 5.8	63 26	 1.25	I.V. glucose and saline + calcium gluconate; symptoms entirely cleared
6	Breech delivery, difficult resuscitation; vomiting, blue spells, shocked	1 9	8.0 10.0	8.1 6.7	82 30	3.1 0.9	I.V. glucose and saline + calcium gluconate; symptoms promptly relieved
7	Difficult delivery; breathing difficulty 2 days; vomiting	28	7.3	7.4	43	1.22	Serum protein, 4.38; I.V. glucose and saline + calcium gluconate; symptoms improved slightly; died—coarctation of aorta
8	Prematurity; convulsions; mother had severe toxemia	1 7	7.9 8.7	5.7 4.9	74 34	3.8 –	I.V. glucose and saline + calcium gluconate; symptoms disappeared
9	Blue spells since birth	5 12	7.6 10.0	5.5 4.8	40 44	1.75 1.6	I.V. glucose and saline + calcium gluconate; symptoms disappeared
10	Breech delivery; listless, drowsy, carpopedal spasm	4 7	7.5 10.3	5.6 4.7	57 29	1.8 1.3	I.V. glucose and saline + calcium gluconate; improved and lost symptoms of tetany; died—sepsis neonatorum; multiple lung abscesses
11	Supposed normal delivery and resuscitation; blue spell at 2 hours of age; cyanosed	5 — 24	7.8	10.7	53	2.75	Spinal fluid—crenated blood; I.V. glucose and saline + calcium gluconate

CASE 10.—Baby M., 4 days of age, with birth weight of 6 pounds, was born by breech presentation. The mother had a pyuria of pregnancy and was never well. The baby was vomiting since birth. He was listless and drowsy and showed a suggestive carpopedal spasm. The baby was jaundiced and had a scanty moist discharge from the umbilicus. Blood serum calcium was 7.5 mg. per cent; phosphorus, 5.6; nonprotein nitrogen, 57; creatinine, 1.8. The baby was given continuous intravenous administration of glucose in saline and 10 c.c. of calcium gluconate repeated in twelve hours. The condition improved and in three days the laboratory findings were calcium, 10.3 mg. per cent; phosphorus, 4.7 mg. per cent; nonprotein nitrogen, 29 mg. per cent; creatinine, 1.3 per cent. The infant continued to be listless, the blood culture was positive for *Staphylococcus aureus*, and he died. Postmortem showed multiple abscess of lungs and bilateral fibrinous pleurisy.

CASE 11.—Baby C. was admitted at 5 hours of age; birth weight, 8 pounds, 10 ounces; labor, normal. He breathed spontaneously and began having blue spells two hours after birth. Physical examination revealed a cyanosed baby with poor air entry into chest. Spinal fluid contained blood and showed xanthochromia. Blood calcium was 7.8 mg. per cent; phosphorus, 10.7; nonprotein nitrogen, 53; creatinine, 2.75 mg. per cent. The baby was given continuous intravenous administration of glucose and saline and calcium gluconate. Five days after admission the calcium was 7.3; nonprotein nitrogen, 42; and creatinine, 1.2.

DISCUSSION

In most of the cases reported the serum calcium was lowered, the phosphorus raised, and the ratio of calcium to phosphorus was decreased in every case. The symptoms were relieved by calcium intravenously. In these cases which we are reporting there is phosphorus and nitrogen retention which indicates deranged kidney function of temporary or permanent nature. In two of our cases there was an extreme form of nitrogen and phosphorus retention due to abnormalities of the kidneys incompatible with life. The symptoms in these were temporarily relieved by calcium gluconate intravenously. In the other cases the disturbed kidney function has been relieved by the treatment. The cause of this disturbed renal function may be oliguria and anuria from insufficient fluid intake. Poor fluid intake was recorded with some of the patients. In many of the cases the delivery was difficult, resuscitation difficult, and evidences of asphyxia and shock in the baby were observed. Toxemia in the mother is recorded in a few. These factors probably contributed to the lack of kidney function which resulted in the retention of phosphate. Hyperphosphatemia tends to lower and decreases the ionization of the serum calcium.

Guild[3] states, "Rare instances of tetany have been reported in the newborn, in that convulsions during the first week or two of life have been accompanied by a low blood calcium and have been relieved by calcium therapy. . . . It is unlikely that these are related to the ordinary variety of infantile tetany, although the actual circumstances leading to the appearance of tetany in the newborn are not clearly understood."

Shelling[4] and Guild[3] report that tetany has been produced experimentally by alkaline phosphate injections. The increased phosphate in

the blood causes a depression of the calcium ions which then brings about the symptoms of tetany. Guild states that in phosphorus retention of nephritis, symptoms of tetany rarely occur due to the relative acidosis, although a situation quite comparable to that experimentally observed is present. She reports tetany associated with nephrosis is due to lowered blood serum protein to which the calcium is adsorbed. We have only one serum protein estimation in our series and it is low.

Shelling[4] states, "Strictly speaking, tetany is not a disease entity but rather a symptom-complex characterized by certain degrees of hyperactivity of the nervous system to stimuli." Shelling gives 5 to 6 mg. per cent as the normal range of phosphorus in infants but then states that it may be as high as 10 mg. per cent in the first few days of life. Phosphorus is increased in active parathyroid tetany, nephritis, overdosage of parathyroid hormone or viosterol, in oliguria and anuria from any cause, and in some cases of infantile tetany. Shelling states that tetany may occur with normal calcium and hyperphosphatemia and it is due to the inactivation of the calcium ions by the excess phosphate.

In the previous reports of tetany of the newborn infant[1, 2] estimations of the phosphorus were not recorded in many cases and the nitrogen retention estimation was not done.

During this period we have observed a few cases of tetany in the newborn infant with normal nonprotein nitrogen and creatinine of the blood.

In summary, these eleven cases show urinary retention of nitrogen and phosphorus associated with a decreased calcium: phosphorus ratio. In many of the cases the symptoms were those which have been associated with what has been called tetany of the newborn infant. The symptoms were relieved by the intravenous injection of calcium gluconate and glucose in saline. It would appear that disturbed kidney function is a cause in some of the cases in the newborn infant in which twitching, convulsions, carpopedal spasm, cyanosis, etc., are seen.

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THE FINGER PUNCTURE METHOD FOR THE SEDIMENTATION RATE

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IN THE past two decades the erythrocyte sedimentation rate has been found useful in medicine for estimating the degree of active infection. Many methods have been proposed for measuring the fall of red blood cells. Until recently, all these methods necessitated venipuncture. It soon became apparent, however, that when frequent determinations were to be made, venipuncture was found to be too cumbersome a method, as well as painful for the patient. This is particularly so in the case of pediatric patients. For that reason some investigators[1, 3] suggested microsedimentation methods in which capillary blood may be used.

It has been pointed out by Hamm and his co-workers[2] and by others[1] that the rate of fall of red blood cells depends upon many technical factors:

a. Height of blood column
b. Interior diameter of sedimentation tube
c. Type of anticoagulant
d. Temperature of room when test is done
e. Inclination of tube
f. Effect of standing

These factors vary widely with each of the proposed methods for measuring the sedimentation rate. In order to evaluate a simplified micro-fingertip method, it is the purpose of this study to compare it with other widely accepted and used methods.

PROCEDURE

The patients presented in this study were girls and boys 6 to 15 years of age who were suffering from rheumatic heart disease. A total of fifty-two children were observed, thirty-three having normal sedimentation rates and nineteen, rapid ones. Fasting blood was collected at one sitting for all methods used in this study. The technique, as well as the technical personnel, was not changed at any time during the entire course of study.

Four methods were compared with our micro-fingertip method. Table I illustrates the technical details of each of these methods.

RESULTS

An analysis of Table II brings into view several noteworthy observations. In the group of children having a normal sedimentation rate, not one instance was found to be outside the range considered normal

From the St. Francis Sanatorium for Cardiac Children.

TABLE I

VARIOUS METHODS FOR MEASURING THE SEDIMENTATION RATE

NAME OF METHOD	TUBE		ANTICOAGULANT	AMOUNT OF BLOOD USED (C.C.)	METHOD OF COLLECTING BLOOD
	BLOOD COLUMN (MM.)	DIAMETER (MM.)			
Wintrobe	100	3	$\frac{2}{3}$ K Oxalate $\frac{}{}$ NH$_4$	1.3	Venipuncture
Westergreen	200	2.5	Sodium citrate 3.8%	1	Venipuncture
Cutler Macro	40	5	Sodium citrate 3%	1	Venipuncture
*Cutler micro-fingertip	40	2.5	Sodium citrate 3%	0.3	Fingertip
Cutler Micro-vein	40	2.5	Sodium citrate 3%	0.3	Venipuncture

*Blood is collected in the usual manner from the index fingertip into a short narrow test tube containing 0.075 c.c. of wet 3 per cent sodium citrate. The amount collected is 0.3 c.c. as measured by a graduated line on the tube. The citrate and blood are thoroughly mixed and drawn into the Cutler sedimentation pipette.

The bottom ends of the pipette are then sealed by a spring cap, and the pipette is suspended in a rack in a vertical position and observed for one hour.

in each of the five methods used. In addition, it is noteworthy that while the degree of fall of red blood cells when measured by various methods runs parallel to the size of the tube used, the average sedimentation rate for the entire group was found to be practically the same in all methods. The obvious conclusion, therefore, is that in measuring the sedimentation rate in children having a normal rate, the various methods are interchangeable. This is particularly true when the three types of the Cutler method are compared.

In the group of children showing a rapid sedimentation rate, the range of fall of red blood cells varies from 15 to 18 mm. in the Cutler method to 12 to 84 in the Westergreen. For this reason the averages in this group of cases are not comparable. It is, however, significant to find that of the entire group of nineteen children having rapid sedimentation rates by the Cutler method, only two showed a normal rate when measured by the Wintrobe and Westergreen methods. But even here the discrepancy is of low magnitude since the two children show only a mildly rapid fall by the Cutler method and a decidedly high normal by the other two methods. Furthermore, in this group of cases the Cutler micro-fingertip and Cutler vein methods are completely interchangeable (Table III).

COMMENT

When repeated determinations of the sedimentation rate are to be made on the same patient, the method of obtaining the blood is of some importance. It is admitted that obtaining blood from the fingertip is more practical and less painful to the patient. Furthermore, patients requiring repeated determination of the sedimentation rates for long periods of time frequently belong to the group of patients who also re-

TABLE II

PATIENTS WITH NORMAL SEDIMENTATION RATE

PATIENT	1 CUTLER MICRO-FINGER-TIP (MM.)	2 CUTLER MICRO-VEIN (MM.)	3 CUTLER MACRO (MM.)	4 WINTROBE (MM.)	5 WESTER-GREEN (MM.)
D. A.	3	3	4	4	4
C. I.	5	5	5	6	6
M. G.	5	6	6	8	9
G. D.	5	5	5	6	5
I. A.	5	5	–	5	7
A. P.	6	5	7	10	7
M. D.	6	5	5	5	7
C. B.	6	7	7	6	7
A. S.	7	6	6	7	3
B. W.	7	7	7	10	8
J. C.	7	7	7	10	7
D. A.	7	6	–	5	6
A. R.	7	5	5	5	5
B. B.	7	7	7	7	7
A. S.	9	9	8	12	8
A. M.	9	8	9	9	5
L. S.	9	8	–	10	7
E. A.	8	8	–	10	11
P. C.	10	9	–	10	7
L. F.	10	7	8	12	11
C. F.	10	9	–	10	10
A. C.	10	9	–	9	7
S. L.	10	10	10	11	10
A. S.	10	11	–	–	12
A. M.	11	10	–	13	14
S. P.	12	10	11	13	9
D. T.	12	11	11	8	12
J. C.	12	12	–	11	12
M. H.	12	12	–	12	8
A. M.	12	11	12	12	12
W. D.	12	10	10	10	15
T. D.	12	10	12	13	15
A. M.	12	12	–	13	15
Average	8.6	8.0	7.7	9.1	8.7
Range	3 to 12	3 to 12	4 to 12	4 to 13	3 to 15
Usual range (normal)	4 to 12	4 to 12	4 to 12	4 to 15	4 to 15
Maximum deviation in millimeters as between Method 1 and other methods		3	2	4	4

quire more important intravenous procedures for therapy. Their veins, therefore, must be saved for this purpose. In addition, not a few children present definite technical difficulties in finding the vein for venipuncture. These are some of the reasons that prompted many investigators to devise a micro-fingertip method.

For study purposes and comparisons, the literature on sedimentation rate presents a chaotic and confusing picture. Many methods are used and various techniques are employed. This state of confusion is true not only in comparative mass studies but also in the follow-up of single

TABLE III

PATIENTS WITH HIGH SEDIMENTATION RATE

	1 CUTLER MICRO-FINGER-TIP (MM.)	2 CUTLER MICRO-VEIN (MM.)	3 CUTLER MACRO (MM.)	4 WINTROBE (MM.)	5 WESTER-GREEN (MM.)
I. M.	15	15	–	18	26
L. S.	15	16	–	16	30
J. P.	15	15	15	22	21
M. J.	15	13	–	12	17
J. C.	16	16	–	16	21
H. D.	16	15	14	12	12
E. P.	16	14	15	16	14
L. M.	17	16	–	24	28
R. H.	17	16	15	16	25
R. A.	17	17	18	29	28
R. R.	18	17	–	25	22
R. R.	19	18	19	34	40
A. I.	20	18	–	32	29
M. V.	21	20	20	35	52
L. M.	22	22	20	43	55
M. R.	22	19	–	28	24
F. S.	23	24	–	30	44
J. O.	27	26	29	43	67
V. M.	28	28	28	38	84
Average	18.8	18.1	19.3	25.7	33.6
Range	15 to 28	13 to 28	14 to 29	12 to 43	12 to 84
Usual range (rapid sedimentation rate)	12 to 30	12 to 30	12 to 30	15 to 50	15 to 100
Maximum deviation in millimeters as between Method 1 and other methods		3	2	21	56

TABLE IV

CUTLER MICRO-FINGERTIP METHOD COMPARED WITH FOUR OTHER METHODS

NAME OF METHOD	UPPER LIMIT OF NORMAL	NORMAL SEDIMENTATION RATE			RAPID SEDIMENTATION RATE		
		NUMBER OF DETERMINATIONS	% COMPARABLE WITHIN ±2 MM.	% COMPARABLE WITHIN ±4 MM.	NUMBER OF DETERMINATIONS	% COMPARABLE	% NOT COMPARABLE
Wintrobe	15 mm. in 60 min.	32	81	100	19	90	10
Westergreen	15 mm. in 60 min.	33	64	100	19	90	10
Cutler Macro	12 mm. in 60 min.	21	100	100	10	100	0
Cutler Micro-Vein	12 mm. in 60 min.	33	96	100	19	100	0

cases. In an institution treating patients referred from many hospitals and clinics, an evaluation of the significance of sedimentation rates on these patients becomes almost impossible. If, therefore, these patients are to be followed up properly, a method is to be standardized which will bear comparison to the various methods used on these patients previously. It would naturally amplify and clarify matters if a unified method could be adopted. The criteria for such a unified method must be practicability and simplicity and should be made as painless as possible. Such a method, in our opinion, is the Cutler micro-fingertip method. This method not only is practicable, simple, and painless, but also shows a high degree of accuracy when compared with all of the more important and accepted methods.

Eighty-one per cent of the readings by the Wintrobe method in the normal group of cases are within ±2 mm. of the readings by the Cutler fingertip method, and the remaining 19 per cent fall within ±4 mm. In the group of children having a rapid sedimentation rate, 90 per cent are comparable in the two methods. A similar situation exists when our method is compared with that of Westergreen. Actually only 64 per cent fall within ±2 mm. of the reading by the Cutler method, but the remaining 36 per cent are all within normal limits. In the group with rapid sedimentation rates, 90 per cent are comparable. When, however, the Cutler micro-fingertip method is compared with the micro and macro Cutler vein methods, the parallelism is practically 100 per cent. (Table IV.)

SUMMARY

1. Fifty-two rheumatic children were studied with regard to the sedimentation rate.

2. Thirty-three of these had normal sedimentation rates when measured by any of five different methods. The correlation between the methods in this group was almost 100 per cent.

3. Nineteen of these had a rapid sedimentation rate by all methods used. The correlation here was 90 per cent.

4. The Cutler micro-fingertip method is presented as a substitute for any of the other methods when repeated determinations are necessary because of its simplicity, practicability, and accuracy.

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SPORADIC CONGENITAL OBSTRUCTIVE GOITER WITH RECOVERY FOLLOWING OPERATION IN A THIRTEEN-DAY-OLD INFANT

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A REVIEW of the literature reveals but few cases of sporadic congenital obstructive goiter with symptoms severe enough to cause death. Nor was the author successful in his search for a method of preoperative treatment, operative procedure, and postoperative management in infants of such early age. Therefore, it was felt that a detailed description as carried out in this case might be of some value.

In order to obtain a clear picture it becomes necessary to discuss the family history in some detail as there were two, possibly three, such cases in this same family. Two died and the third one was operated upon and is doing well. Mrs. S., aged 29 years, has been married for eleven years. She was born in Yugoslavia and has lived in Canada for the past thirteen years. Her husband, aged 38 years, was also born in Yugoslavia and has lived in Canada for fifteen years.

There have been seven children born to this couple, and five are still alive. The first three were normal full-term males and are now 11, 10, and 7 years of age, respectively. All the deliveries were at the Vancouver General Hospital.

The mother developed severe asthma in 1934 from some unknown cause, and she still has severe attacks at times, although she states they are less frequent. She administers adrenalin injections at home during these attacks. Her weight is 116 pounds, but prior to the onset of asthma it was 150 pounds. She has a centrally placed thyroid swelling of small to medium size which appears to be adenomatous in character. It has been present since before marriage, and she has never received treatment for it.

CASE 1.—Male (fourth child), born Oct. 15, 1936. Delivery was normal, but the child was premature. Weight was 2,350 Gm. (5 pounds, 3 ounces).

At the time of birth the mother was acutely distressed with an attack of asthma and adrenalin had to be given.

Immediately following birth the infant was dyspneic and cyanotic. A large bilateral mass connected by a smaller central one occupied the greater part of the anterior neck but appeared to be situated higher than one would expect the thyroid gland to be. The lateral mass on each side reached to the anterior margin of the sternomastoid muscle, and each lateral part measured 4 cm. in diameter. It was firm, more or less rounded, and slightly movable.

Presented before the Clinical Section of the Vancouver Medical Association at St. Paul's Hospital, Vancouver, Feb. 17, 1942.

From the Department of Pediatrics, Vancouver General Hospital.

There was marked indrawing of the intercostal spaces and retraction of the lower chest wall. There was also a firm edema of the superficial tissues of the lower and upper extremities, the lower anterior abdominal wall, and genitals. Otherwise the physical examination at birth was negative.

The condition of the child on arrival in the nursery from the receiving room was not good. There was considerable mucus in the throat which was troublesome. The child was placed in an incubator and oxygen was administered continuously. During the next three days there was little change, and on the fourth day breast milk was taken. During this time members of the surgical staff saw the child but did not suggest surgical interference. The urinary findings and blood counts were normal.

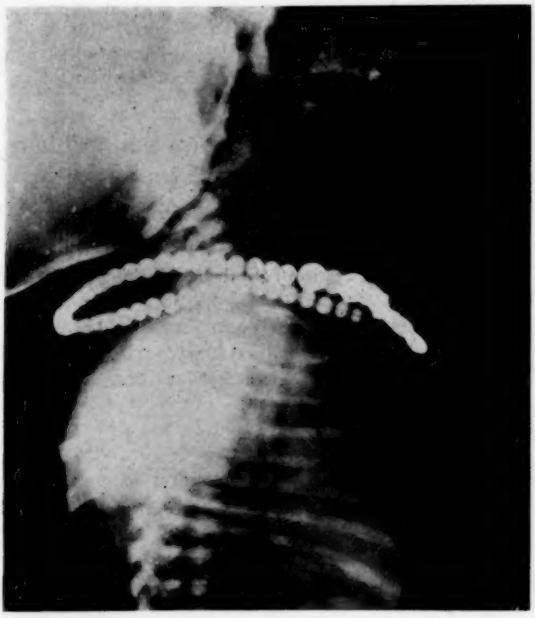

Fig. 1 (Case 1).—Shows the forward displacement of the trachea in the neck by the mass behind it. The radiologic report did not favor an enlarged thyroid as the cause of the displacement, nor did the surgeons suggest operative interference. The child's condition was anything but good and added to this was the unfamiliar picture which presented itself.

Roentgenographic findings (Dr. B. J. Harrison, radiologist) on the fourth day were as follows: There was a large soft tissue swelling in the neck which displaced the posterior wall of the pharynx markedly forward. It extended laterally on either side of the hypopharynx and anteriorly so as practically to surround it. The upper part of the trachea had been displaced forward also, and the laryngotracheal junction was considerably deformed.

The impression gained was that a large mass with more or less spherical nodules arose in the retropharyngeal tissues and extended forward on either side of the trachea as well as the larynx. It did *not* suggest a thyroid. Examination of the body and limbs presented no evidence of osseous abnormality. There appeared to be some relative atelectasis of the lungs.

On the ninth day it became necessary to gavage the child because of difficulty in swallowing. The extremities were still firm from the edema.

On the twelfth day the weight was only 2,200 Gm.; temperature, 99 to 101° F., respiratory distress was marked.

On the thirteenth day the general condition was poor. Breathing became more shallow and rapid and the child died at 12:35 P.M.

Autopsy Report.—There was a swelling in the neck which proved to be the thyroid gland. A number of sections were taken through the gland which showed very marked hyperplasia and hypertrophy of the acini. They were tortuous and enlarged for the most part; very few contained colloid material. The epithelium generally was of a high columnar or cubocolumnar type and frequently thrown into intra-acinar papillary infoldings. This is a very definite picture of marked hyperplasia and hypertrophy.

Diagnosis (H. H. Pitts, pathologist).—The diagnosis was marked congenital hyperplasia and hypertrophy of the thyroid. There is nothing particularly remarkable in the section through other organs beyond a diffuse but early bronchopneumonic process throughout both lungs.

The next two children born to this mother presented interesting findings. However, these children were not seen by me in the newborn period, and the case history of each was obtained from the record office of the hospital.

On Aug. 28, 1938, a full-term, healthy male (fifth child), weighing 7 pounds, 5 ounces, was born.

On the eleventh postnatal day (September 8) a swelling was noticed on the right side of the neck. From the description given, it was probably a comparatively small mass. The remainder of the neck was free from swelling. However, on this same day the child developed cyanosis and dyspnea. Physical examination revealed some enlargement of the heart but no murmur. Mention was made of some edema of the face and ankles.

Roentgenographic findings on September 9 were as follows: There was marked enlargement of the heart and enlargement of the supracardiac shadow. The child received a treatment for the enlarged thymus. There was no displacement of the trachea.

On September 11 respirations became difficult, and the child was placed in an oxygen tent. Cyanosis occurred when the infant was removed from the tent. Edema of the face, scrotum, and extremities was present by this time. Feedings were taken fairly well.

On September 15 respirations were rapid and shallow, and the child choked readily. During the next few days he became cyanosed during feedings. Temperature rose to 101° F. (rectal) for two days, during which time diarrhea was present.

On September 24 dyspnea and cyanosis were severe. There was no mention of the swelling in the neck having enlarged further. Temperature rose to 104° F., and the child died at noon.

Comment.—In many respects this case resembled the preceding one. Although the swelling in the neck was unilateral and apparently smaller anteriorly, on viewing the x-ray films taken on September 9 there appeared to be a slight forward displacement of the trachea in the neck. Had a second examination by x-ray been made at a later date, one would have expected considerable forward displacement, based on the findings in the first case, plus the symptoms which this child presented.

In 1939 the mother became pregnant again and attended the prenatal clinic at the hospital. It was decided to terminate her pregnancy and perform an operation for sterilization. Apparently this decision was made because of her asthma, and perhaps the fate of her last two infants had some bearing on the case. However, the mother refused this advice. She was then started on iodine therapy. After the third day no further iodine was taken because the mother complained that it made her asthma worse. She was allowed to continue her pregnancy. On Feb. 11, 1940, she gave birth to her first female child (sixth child). The delivery was normal. Birth weight was 3,315 Gm. There was no record in the case history of any enlargement in the neck or other signs or symptoms similar to those previously described. Her stay in hospital was uneventful. I saw this child in February, 1942. She was then 2 years of age and normal in every way. On Feb. 16, 1942, the epiphyseal age of her wrists was approximately three years.

It is difficult to explain why this child escaped the fate of the previous two infants and the near-similar fate of the infant whose history is about to be given and which forms the basis of this article. The mother was not taking any form of treatment, there was no change in residence or diet, and she was not taking iodized salt. The fact that she was under clinic supervision may have influenced her to take more rest, thus relieving some of the strain on her thyroid gland. It does not seem likely that three days of iodine therapy could have produced such results. However, she was under supervision of the clinic during her next pregnancy (seventh), and yet she gave birth to a child who in all respects resembled the previous male children herein described.

CASE 2.—Male child (seventh), born on Nov. 22, 1941. Full term, normal delivery; birth weight, 3,200 Gm. (7 pounds, 3 ounces). Condition was good on arrival at the nursery.

However, there was a large bilateral, firm, rounded, somewhat movable mass in the neck. This was connected by a thickened band, the whole mass suggesting an enlarged thyroid gland. It was situated somewhat higher in the neck than one would expect, as the upper border of each lateral lobe was but a short distance below the angle of the mandible on either side. The diameter of each lateral mass was approximately 4 cm., and the width of the isthmus was 2 cm.

The heart sounds were normal except for a loud systolic murmur, best heard over the precordium in the third left interspace. The cry was lusty. There was no edema of the face or extremities as mentioned in the previous cases.

With the arrival of the child in the nursery, I was determined that if at all possible this child would not be allowed literally to choke to death, as happened to the infant in Case 1, if it could be prevented. Therefore, it was decided to start iodine therapy at once and to consider from the onset the probability of surgical interference in the event of pressure signs.

As previously mentioned, a recognized form of procedure in such cases was lacking in available literature. It is true that there was mention of the use of iodine ointment for rubbing on the swelling daily or the use of iodine internally. There was mention of how rapidly such enlargements would "melt" under iodine therapy in the ordinary enlargements which one sees from time to time. However, it was

difficult to see how such a large swelling which caused pressure symptoms as mentioned in Case 1 could be brought under control before causing death of the infant. The infant in Case 2 presented an enlargement as great as did the infant in Case 1 but without pressure symptoms. The lack of pressure symptoms was due to an incomplete encirclement of the trachea.

Thus, ⅓ gr. of sodium iodide in aqueous solution was started by mouth once a day, beginning on the third day of life.

On November 25 (third day) the baby was doing well with no change in size of the swelling nor was there any respiratory distress.

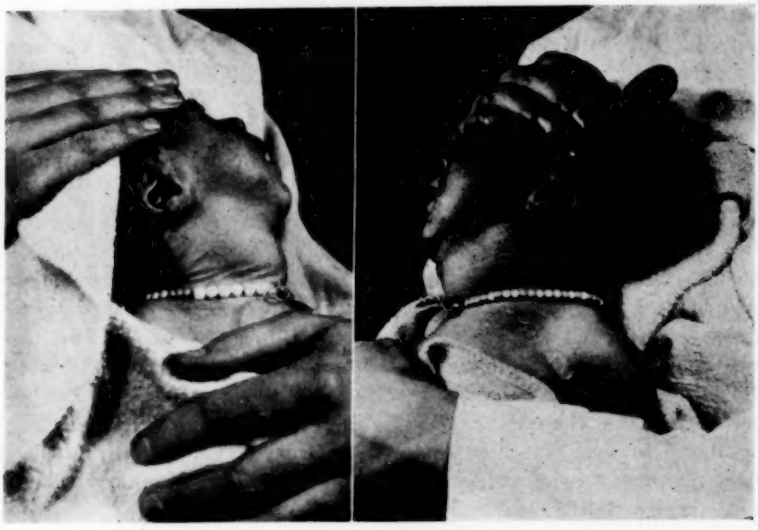

Fig. 2 (Case 2).—Lateral views of enlarged thyroid gland taken on the fourth day of life.

Roentgenographic findings (Dr. B. J. Harrison) were as follows:

On examination of the thoracic inlet and neck, the trachea appeared to be grossly displaced forward at the junction of the larynx, this space appearing to be approximately the size it normally is in the adult.

It gives the impression that the mass palpable in the neck extends behind the esophagus and trachea.

On November 29 there were no symptoms. The baby was taking feedings well. However, the swelling in the neck appeared to be enlarging slightly.

Surgical consultation (Dr. T. H. Lennie) was as follows:

If signs of compression develop in the neck, exploration should be done. In the meantime increase the sodium iodide to ⅓ gr. three times a day.

On November 30 the sodium iodide was increased as suggested. The face became cyanosed when the child cried.

Roentgenographic findings on December 1 were as follows:

The cardiac shadow was definitely enlarged and the pulmonary markings running toward the upper left apex were more prominent than usual. The apex of the heart was more protuberant than normal and gave the impression of a congenital lesion.

On December 1 the child was rather listless at times. Slight stridor was now noticeable on crying, and there was considerable gurgling in the throat.

On December 2 listlessness was more noticeable. The child cried very little, but when he did, cyanosis was more evident. Breathing was somewhat noisy and labored, and there was some difficulty in swallowing.

Laboratory report on the mother who was given 40 Gm. galactose was as follows: In one-half hour the test showed 52 mg. of galactose per 100 c.c. of blood. In one hour the test showed 27 mg. of galactose per 100 c.c. of blood. Blood calcium was 12.3; blood phosphorus, 10; basal metabolic rate, minus 8; blood cholesterol, 210.

On December 3 cyanosis and stridor were becoming more marked, and the mass in the neck appeared to be enlarging and somewhat firmer. The child now weighed 3,070 Gm., and this was the first gain in weight from the low initial weight loss. It was decided to operate.

On December 4 thyroidectomy was performed as follows by Dr. T. H. Lennie: Under intratracheal ether anesthesia the usual collar incision was made, the flaps dissected, and the fascia and muscles divided longitudinally. Retraction exposed a large thyroid isthmus together with enlarged right and left lobes. Between mosquito hemostats the isthmus and a portion of both lobes were resected and the trachea freed. All bleeding points were well tied. There was a nodule on the right side about the size of a golf ball which was lying posterior and lateral to the trachea. This was delivered by Lahey forceps. After consultation with the anesthetist, who expressed the opinion that the child was quite pale, it was decided to discontinue the operation and either trust to iodine to shrink the remaining portion of the gland or to remove this nodule at a subsequent operation. A small Penrose drain was inserted into the wound, the muscle closed with fine catgut and the skin with dermal catgut. A blood transfusion followed the operation.

Pathologic Report (Dr. H. H. Pitts).—

Macroscopic Examination: Specimen consisted of a piece of thyroid tissue weighing 6 Gm. and measured 4 by 2.5 by 1.5 cm. On section it presented a homogeneous, reddish brown, moderately firm, glistening cut surface.

Microscopic Examination: A number of sections were taken at different levels through the gland and it consisted of larger and smaller acini, practically all containing colloid material and lined by single layers of cuboidal epithelium. In a considerable number of instances there were definite papillary infoldings of the lining epithelium suggesting previous hyperplasia. Some of the acini were quite dilated, almost cystically dilated, and there were a few rather broad fibrous bands interspersed throughout in which some lymphocytic infiltration was present.

The histologic picture was somewhat suggestive of a subinvolution stage in a previously hyperplastic thyroid gland.

Diagnosis.—The diagnosis was subinvolution stage in a previously hyperplastic thyroid. Dr. Pitts, the pathologist, stated that had he been given the slides to interpret without knowing the source of the material before him he would have said without any hesitation that the condition was undoubtedly Graves' disease.

Postoperative Course.—On December 4 the patient returned to the ward in good condition. The color was good and the child received oxygen through a nasal catheter. Blood transfusion of 110 c.c. of citrated blood was given, and tincture of camph. co., 10 minims, was given that evening. The patient was placed in the Fowler position with a neck pillow.

Mistura sodii iodidi (1 gr.) was started at midnight, then ⅛ gr. given three times daily.

A catheter and laryngoscope were kept by the child's bed in case of sudden respiratory difficulty.

On December 5 the temperature rose to 101° F. Glucose water was taken well. Temperature rose to 103° F. but was normal by the third day.

Excess mucus was removed from the throat by the electric suction pump as the baby became cyanosed at times. An oxygen tent was used when cyanosis became evident.

On December 7 fluids were taken well and without difficulty. An evaporated milk formula was started. The stools were inclined to be loose during the next two weeks.

On December 9 weight was 3,040 Gm. The weight remained stationary for the next ten days, probably due to the loose stools. The child's general condition was improving steadily.

On December 25 the weight was 3,200 Gm. The baby was doing well except that the incision was slow in healing.

Fig. 3 (Case 2).—Lateral and posterior views taken on February 4, 1942. Shows complete healing of incision.

On January 4, 1942, sodium iodide was discontinued and Lugol's solution, 2 minims, was given daily. The swelling on the right side had diminished under sodium iodide treatment until it was now but about one-half the size of that following operation. The left side showed similar change in size. Drisdol, 2 minims, was given daily. The formula was now changed to 2 per cent diluted boiled milk mixture because the stools showed a tendency to be loose again.

On January 7 the weight was 3,420 Gm. which showed a nice gain since December 25. The child was doing well in every way.

On February 4 the child was still in the hospital. This was probably not entirely necessary but we wished to keep this infant under close observation for a considerable length of time. He was discharged Feb. 4 from hospital weighing 4,075 Gm.

On February 16 the child was doing well at home. Lugol's solution was discontinued as from this date, as the remaining thyroid tissue had been appreciably reduced.

The most interesting fact in the family history was the relationship of sex to the presence of congenital goiter. All the male children, commencing at the fourth pregnancy, were affected, while the female child (sixth pregnancy) is still free of signs and symptoms.

It is perhaps not difficult to explain why the mother gave birth to her first three male children without symptoms developing. Until the fourth

Fig. 4 (Case 2).—Shows lateral and anterior views of the healed incision at 9½ months of age. Note general well-being of the child.

pregnancy her thyroid was probably functioning satisfactorily. Yet how did the girl escape the fate of her two brothers? (See Table I.)

TABLE I

PREGNANCY	SEX	AGE	PRESENT STATUS
First	Male	11 yr.	Alive and well
Second	Male	10 yr.	Alive and well
Third	Male	7 yr.	Alive and well
Fourth	Male	13 days	Died (Case 1)
Fifth	Male	27 days	Died
Sixth	Female	2 yr.	Alive and well
Seventh	Male	8 mo.	Alive and well following operation (Case 2)

A somewhat similar family history is presented in Table II.

TABLE II*

PREGNANCY	SEX	PRESENT STATUS
First	Male	Stillborn (in Germany)
Second	Female	Living and well
Third	Male	Died at 8 weeks of age (convulsion)
Fourth	Male	Died at 9 weeks of age (convulsion)
Fifth	Female	Living and well
Sixth	Female	Died in adult life from brain tumor (born in Canada)
	Male	Died at 5 months of age (convulsion)
Seventh	Male	Born with congenital thyroid enlargement
(Twins)		Died in second convulsion thirty-six hours after birth
Eighth	Female	Died in utero about twenty-fourth week of pregnancy
Ninth	Male	Living and well (now in Air Force)
Tenth	Male	Living and well (now in Air Force)
Eleventh	Female	These twins are living and well
	Female	

*I am indebted to Dr. W. D. Patton of Vancouver for submitting to me the case records as seen in this table.

Mrs. F. H. (see Table II) arrived in Canada in 1910 from Germany. She had always been overweight and of the hypothyroid type.

Between the eighth and ninth pregnancies Mrs. F. H. developed marked exophthalmic goiter symptoms of tachycardia, tremor, and exophthalmos and had partial thyroidectomy (May, 1915).

Although Table II is not conclusive evidence in that one cannot be sure what caused the death of each male child, it was thought to be an interesting series in that one male child (seventh pregnancy) definitely had congenital thyroid enlargement and died in convulsion. All previous male children in this family had died of a convulsion of unstated cause, whereas each female child survived. It was not until the mother developed a hyperthyroidism following a hypothyroidism and had her goiter removed that she gave birth to living male children.

Might not the laws of genetics as they apply to human heredity account for the findings summarized in Table I and perhaps also those in Table II?

DISCUSSION

Probably the foremost thought in the mind of the reader at the present moment is: What will be the outcome of having removed part of the thyroid in this infant? Frankly, one cannot say, but when faced with a thyroid enlargement which practically surrounds the esophagus and trachea, and which has caused death in one, if not in two brothers, by pressure asphyxia, and the third child is threatened with the same fate, one has little time to consider the ultimate result. The main objective was to save the child's life. For several years it will be essential that the child be under close observation for any sign of thyroid disturbance. Myxedema must be considered very carefully, and one must be on guard against such an eventuality, in which case thyroid extract will have to be administered. On the other hand, Lugol's solution may have to be given from time to time if hyperactivity occurs.

Following operation, it was suggested that anatomically and physiologically it might have been better to have incised the deep fascia, remove the portion of the gland lying posterior to the trachea from that position, thus relieving pressure symptoms, suture the skin, then give adequate amount of iodine in some form to "melt" away the excess gland tissue, as iodine is the well-recognized treatment in the nonobstructive simple enlargement in newborn infants. This suggestion might be well worthy of consideration if a similar condition were to present itself again.

Solis-Cohen and Steinbach,[1] in 1939, described a similar case in an infant born with a large bilateral moderately firm mass in the neck. The clinical picture of dyspnea, cyanosis, and refusal to nurse was present. The mother presented no evidence of a visible goiter, but her appearance and intelligence suggested a hypothyroid constitution.

The infant died in less than forty-eight hours following birth, and at autopsy the thyroid gland was found to have encircled both the trachea and esophagus.

Mitchell and Struthers,[2] in 1933, reported a case in most respects like those presented in this article, except that the child was apparently normal until 6 weeks of age. The parents refused operation so tracheotomy was performed. The child was later found dead in bed. In this case symptoms preceded visible neck swelling.

Skinner, of Yakima, Wash.,[3] in 1924, reported twelve cases of congenital goiter in newborn infants. In every case the mother had a simple goiter, and there is no mention of any infant having developed obstructive symptoms. Apparently these infants recovered under iodine therapy. In discussing my cases with Dr. Skinner in January, 1942, the impression gained was that he had not encountered the severe obstructive type herein described.

In British Columbia, which is just north of the state of Washington and 250 miles from Yakima itself, it was, at the time of Dr. Skinner's

article, and still is, unusual to see congenital thyroid cases. Of late years the almost universal prophylactic use of iodine given to the pregnant mother accounts for the rarity of this condition in all probability.

SUMMARY

1. But few cases of congenital hypertrophy of the thyroid with pressure symptoms severe enough to cause death have been reported. Two such cases are herewith presented.

2. A method of preoperative treatment, operative procedure, and postoperative management as carried out in the infant in Case 2 is given in detail.

3. Visible swelling in the neck is present in most cases when symptoms appear but not always (Mitchell and Struthers' case[2]). One should not neglect an x-ray of the trachea (lateral view) in dyspnea and cyanosis of the newborn where the cause has as yet not been established.

4. Death is due to pressure asphyxia by encroachment on the trachea. Surgical removal of that portion of the thyroid gland lying posterior to the trachea was found necessary in this case, as iodine therapy was considered to be inadequate treatment in such a rapidly progressing condition. Iodine therapy should be reserved for "melting" the gland after removal from its dangerous position.

5. Constant postoperative attention is imperative for several days. An oxygen tent should be in the room in case of cyanosis, an electric suction pump is indispensable for sucking mucus from the throat, and above all, a catheter and laryngoscope must be at hand for immediate use by a capable assistant in case of sudden respiratory difficulty.

6. It is now several months since the child had his operation. There is no evidence of thyroid disturbance, but periodic examination for several years will be necessary to guard against possible dysfunction of the remaining gland substance.

I wish to express my deep appreciation for the interest, splendid cooperation, and surgical care given the infant in Case 2 by Dr. T. H. Lennie of the surgical staff. The child is now over 1 year of age and normal in every way (December, 1942).

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THE FAMILIAL EPIDEMIOLOGY OF RHEUMATIC FEVER
GENETIC AND EPIDEMIOLOGIC STUDIES

II. Epidemiologic Studies

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THE AGE RISK IN RHEUMATIC FEVER

THE characteristic age expression of rheumatic fever may be designated as "age susceptibility." In many infectious diseases, age susceptibility is more apparent than real, representing or reflecting exposure or subclinical infection. For example, although measles is considered a disease of childhood, it is well known that adults who are not immune develop the disease with equal frequency following exposure. It is more commonly observed that the school child contracts measles and exposes the susceptible younger members of the household.[35-38] In marked contrast to the usual picture in a communicable disease, in rheumatic fever primary and secondary cases have similar ages of onset.[12, 38]

It has been shown in the previous genetic studies that predictions made in earlier calendar years were not realized until the siblings had reached the age-susceptible period. It therefore is apparent that the age expression of rheumatic fever must be taken into account in genetic and epidemiologic analysis. In order to analyze the factor of age in the pattern of spread of rheumatic fever in the families studied, it was necessary to derive a numerical measure of age incidence. For this purpose, a representative, accurate, and sufficiently extensive sample was required. Since published data on ages of onset of rheumatic fever in childhood did not meet the requirements specified, an independent sample which seemed suitable was selected.

The characteristics of the standard series from which the age incidence factors are derived determine the limitations of their application. The number of onsets expected at specific times and circumstances in any rheumatic series may be estimated provided that the series under analysis has been shown to be consistent with the standard sample. For the standard sample the records of 688 cases were selected from the files of the Children's Cardiac Clinic of the New York Hospital. Rigid criteria were followed in the selection of these cases.

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TABLE X

CHARACTERISTICS OF THE STANDARD SAMPLE OF 688 CASES

CALENDAR YEAR	NUMBER OF SIBLINGS BORN IN EACH YEAR	MEAN AGE	NUMBER OF SIBLINGS HAVING ONSETS EACH YEAR	MEAN AGE
1905	3	6.0	–	–
1906	2	9.5	–	–
1907	8	5.9	–	–
1908	10	8.5	2	2.0
1909	12	8.9	–	–
1910	10	6.0	–	–
1911	13	8.7	3	4.0
1912	17	6.9	2	5.5
1913	22	6.6	4	5.0
1914	23	7.3	6	4.7
1915	21	7.2	9	5.3
1916	30	7.1	11	5.4
1917	22	6.9	11	5.6
1918	35	6.7	13	7.4
1919	30	6.5	10	5.8
1920	33	5.2	18	6.6
1921	47	6.6	28	7.5
1922	35	6.2	32	6.3
1923	39	5.2	40	6.0
1924	36	5.6	28	6.2
1925	44	5.8	34	6.2
1926	31	6.1	49	6.1
1927	24	5.3	38	5.6
1928	33	5.4	42	5.8
1929	35	5.1	45	5.9
1930	24	4.2	38	6.2
1931	13	5.2	31	5.4
1932	13	4.5	27	6.4
1933	15	3.3	32	5.7
1934	–	–	40	5.8
1935	6	2.0	34	6.0
1936	2	2.5	28	6.5
1937	–	–	14	5.8
1938	–	–	12	5.6
1939	–	–	6	7.3
1940	–	–	1	9.0

GROUPED YEARS	MEAN AGE BY YEAR OF BIRTH	MEAN AGE BY YEAR OF ONSET
1905-1925	6.5	6.2
1926-1935	5.0	5.9
1936+	2.5	6.3

The cases used included:

1. All children observed from birth.

2. All children seen in the clinic and diagnosed as nonrheumatic one year or less before onset.

3. All children first observed at onset, if the accuracy of their previous history and their current physical findings warranted the conclusion that this was their first manifestation of the disease.

4. Children observed subsequent to onset in whom physical findings at first examination and the accuracy of their historic information warranted the acceptance of their stated age at onset. Judgment as to accuracy of historic information was based on the adequacy of the medical records available for the period prior to observation in the clinic.

To the best of our knowledge, the onsets of these cases were accurate within a year. There was no preferential selection of cases with younger ages at onset. Any

record which fulfilled the criteria above was selected, so that the sample could be considered a random one, exclusive of adult onsets. In the entire group, with the exception of one child who had a recorded onset at 15 years of age, the ages at onset ranged from under 1 year to 13 years. Therefore the age span which was considered ranged from 0 to 13+ years.

The age at onset was estimated to the nearest month and cases were recorded by the *year* of birth, regardless of the month of birth. For example, a child having an onset at any time from the age of 6 years and no months to 6 years and 11 months and 29 days was considered 6 years of age at onset. By this method it was possible to determine the number of onsets occurring during each entire year of life.

The number of children *born* in each calendar year and the number of children having *onsets* in each calendar year are recorded in a form which should facilitate the use of this series in comparable studies (Appendix, Table XVI).*

A summary of the number of rheumatic children born in each calendar year and having onsets in each calendar year is presented in Table X. It will be observed that for children having onsets in any calendar year, the mean age at onset is approximately 6 years. When the same series was analyzed according to year of birth, however, there was a gradual decrease in the mean age at onset.

The older ages of onset in the oldest group (born between 1905 and 1925) may be attributed to the fact that in the majority of instances the recorded age at onset was historic rather than observed. The youngest group (born after 1936) obviously includes only those children who had onsets before the age of 4 years, since selection of the sample terminates in 1939. There is also to be taken into consideration the probability that although diagnostic criteria were uniform, a gradual increase in the accuracy of diagnosis over the years is to be expected.

This gradual fall in mean age at onset over a thirty-year period does not invalidate the use of this series as a standard sample, provided that the samples to which it is applied are first tested for consistency with it.

DERIVATION OF AGE FACTORS

Several types of age factors may be derived from the distribution of the onsets of the 688 cases, varying only in the type of sample to which they are applicable and the type of information which is desired. Obviously, these factors may be used only in a series of rheumatic children (susceptible children).

Age Incidence Factor.—The case incidence at any age with respect to the total cases in the sample describes the distribution of onsets in the series of 688 rheumatic children. It is obtained by dividing the number of cases occurring at each age by the total number of cases (688). This age factor may be applied to a series of susceptible children to determine how many cases out of the total number of susceptible children available in any sample would be expected to have onsets at each age. For example, in Table XI, A, it may be seen that 15 per cent of a sample should have onsets *at* the age of 6 years.

Cumulated Age Incidence Factor.—Derived directly from the case incidence *at* each age is the cumulated case incidence. It describes the number of children who had onsets *by* each specified age in the total sample. It is obtained by dividing the total number of cases which

*All Appendix tables will appear in the reprint.

occurred *by* any age from under 1 year to 13+ years by the total number of cases (688). This factor may be applied to a series of susceptible children at their current age to determine how many of them would be expected to have had onsets by any specified age. For example, in Table XI, B, it may be seen that 59 per cent of a sample of susceptible children would be expected to have had an onset by the time they were 6 years of age.

Age "Attack Rate" Factor.—The third type of factor is the "age attack rate" factor, which is the ratio of cases coming down at any age to the total number of susceptible children who entered that age unaffected. This is derived by dividing the number of cases occurring at each age by the total number of children who were still unaffected when they reached that age. This is applicable to a series of susceptible children at their current age, provided that cases are recorded at onset, so that in any year the number of susceptible children who entered that age unaffected may be obtained. For example, in Table XI, C, it may be seen that 27 per cent of the susceptible children reaching the age of 6 unaffected in a sample would be expected to have had onsets before the age of 7 years.

TABLE XI

AGE FACTORS DERIVED FROM STANDARD SAMPLE OF 688 CASES

AGE*	0	1	2	3	4	5	6	7	8	9	10	11	12	13+
Age Incidence Factor														
Number of cases at each age	2	14	39	60	87	103	104	82	64	66	39	17	8	3
A. Per cent of cases at each age†	0.00	0.02	0.06	0.09	0.13	0.15	0.15	0.12	0.09	0.10	0.06	0.02	0.01	0.00
Cumulated Age Incidence Factor														
Number of cases by each age	2	16	55	115	202	305	409	491	555	621	660	677	685	688
B. Per cent of cases by each age‡	0.00	0.02	0.08	0.17	0.29	0.44	0.59	0.71	0.81	0.90	0.96	0.98	1.00	1.00
Age Attack Rate Factor														
Number of children entering each age negative	688	686	672	633	573	486	383	279	197	133	67	28	11	3
Number of cases at each age	2	14	39	60	87	103	104	82	64	66	39	17	8	3
C. Age attack rate§	0.00	0.02	0.06	0.09	0.15	0.21	0.27	0.29	0.32	0.50	0.58	0.61	0.73	1.00

*Cases are entered at their age of onset computed as follows:
0, under 1 month to 11.9 months
1, 1 year to 1.9 years
2, 2 years to 2.9 years, etc.

†Computed by dividing the number of cases *at* each age by 688.

‡Computed by dividing the total cases occurring *through* each age by 688.

§Computed by dividing the number of cases occurring at each age by the total number of cases who entered that age negative.

TABLE XII

APPLICATION OF AGE FACTORS TO A SAMPLE OF SUSCEPTIBLE CHILDREN AT SPECIFIC TIMES

AGE INCIDENCE FACTOR APPLIED AT THE TIME OF ONSET OF ALL CHILDREN

AGE	NUMBER OF CHILDREN	AGE FACTOR	CASES		DIFFERENCE
			EXPECTED	OBSERVED	
0	–	0.00	0.00	–	–
1	2	0.02	3.50	2	+1.50
2	9	0.06	10.50	9	+1.50
3	12	0.09	15.75	12	+3.75
4	20	0.13	22.75	20	+2.75
5	30	0.15	26.25	30	–3.75
6	34	0.15	26.25	34	–7.75
7	17	0.12	21.00	17	+4.00
8	14	0.09	15.75	14	+1.75
9	16	0.10	17.50	16	+1.50
10	10	0.06	10.50	10	+0.50
11	5	0.02	3.50	5	–1.50
12	1	0.01	1.75	1	+0.75
13+	5	0.00	0.00	5	–5.00
Total	175		175.00	175	

APPLICATION OF THE THREE AGE FACTORS

The validity of the age factors derived from the standard sample was determined by applying the factors to a series of children known to be susceptible; that is, the affected children in our series of rheumatic families. It was first necessary to determine whether the distribution of onsets among the cases in the family sample was consistent with the standard sample. A test for significance was accordingly made, and it was found that there was no significant difference in the age constitution of the two series (Appendix, Table XVII).

The family data demonstrated a similar range in ages of onset. The children born in early calendar years had the oldest ages of onset, and the youngest children had early ages of onset. This was due to the same selective factors that were operative in the standard sample. There was a significant difference between the two samples in the *number* of case onsets occurring in the specified time intervals, due to the manner in which the rheumatic families were selected. This difference did not invalidate the application of the standard sample to our data since it only concerns the distribution of cases over a period of years and does not refer to their ages at onset.

The determination of case onsets on an age basis involves the use of "proved susceptible children." The 215 cases in the family sample all could be considered susceptible since they all had onsets by the end of the study. Of these, only 175 who were present in the families at the time of onset of the first case were used in order to provide a numerically unchanging sample on which to trace time and age effects.

The Age Incidence Factor: The distribution of onsets in the sample of 175 children was predicted and compared with the actual cases at onset (Table XII). It is apparent that since the specific factor for each age is applied to the *total* sample of 175 children, the adequacy

TABLE XIII

APPLICATION OF AGE FACTORS TO A SAMPLE OF SUSCEPTIBLE CHILDREN AT SPECIFIC TIMES

AGE	A. CUMULATED FACTOR APPLIED IN CALENDAR YEAR 1930					B. CUMULATED FACTOR APPLIED IN CALENDAR YEAR 1939				
	NUMBER OF CHILDREN	AGE FACTOR	CASES		DIFFERENCE	NUMBER OF CHILDREN	AGE FACTOR	CASES		DIFFERENCE
			EXPECTED	OBSERVED				EXPECTED	OBSERVED	
Unborn	1	–	–	–	–	–	–	–	–	–
0	4	0.00	0.00	–	–	–	0.00	–	–	–
1	10	0.02	0.20	1	–0.80	–	0.02	–	–	–
2	4	0.08	0.32	–	+0.32	–	0.08	–	–	–
3	11	0.17	1.87	1	+0.87	–	0.17	–	–	–
4	10	0.29	2.90	5	–2.10	–	0.29	–	–	–
5	14	0.44	6.16	7	–0.84	1	0.44	0.44	1	–0.56
6	20	0.59	11.80	12	–0.20	2	0.59	1.18	2	–0.82
7	16	0.71	11.36	12	–0.64	–	0.71	–	–	–
8	15	0.81	12.15	13	–0.85	2	0.81	1.62	2	–0.38
9	9	0.90	8.10	7	+1.10	6	0.90	5.40	6	–0.60
10	14	0.96	13.44	12	+1.44	12	0.96	11.52	12	–0.48
11	9	0.98	8.82	9	–0.18	9	0.98	8.82	9	–0.18
12	8	1.00	8.00	8	–	8	1.00	8.00	8	–
13+	30	1.00	30.00	30	–	135	1.00	135.00	135	–
Total	175		115.12	117		175		171.98	175	

of the method is determined by the agreement between expected and observed values at each age. In most instances there is close agreement, although some sampling fluctuations were observed. It was concluded that the age incidence factor describes the distribution of onsets in the series of 175 cases adequately.

This age factor may be used for any series of susceptible rheumatic children. Lack of agreement, provided that the sample is consistent in all other respects, might be due to inaccuracy in recorded ages of onset, differences in diagnostic criteria, or, more significantly, to the influence of possible etiologic factors in the disease.

Cumulated Age Incidence Factor: The cumulated age incidence factor is of use in estimating the number of susceptible children who would be expected to be affected *by* each age at any specified time. The number expected would be less at younger age levels and higher at older ones because of the characteristic onset pattern of the disease.

In Table XIII, A and B, there is presented the application of the cumulated age factors to the sample of 175 susceptible children in two arbitrary calendar years (1930 and 1939). The agreement between expected and observed cases is adequate in both instances.

In the year of final observation (1939), when all the children had already become cases, the range in age is small. These results indicate that the cumulated age factor may be used to predict the number of susceptible children who will become cases by the time they reach a specified age in any arbitrary calendar year.

Age Attack Rate: The age attack rate factor may be used to predict the number of cases occurring at a given age in a group of susceptible children negative at the beginning of that year of life; in other words, the risk of attack for susceptible children at specific ages. Table XIV shows the application of the age attack rate factor to the sample of 175 susceptible children present in the families at the time of onset of the primary case. It will be noted that the number of susceptible children who entered each age unaffected was recorded, and since it is assumed that the children who leave the study at each age are present for an average of one-half year, a correction similar to that used in attack rates was introduced. The corrected number of children available is multiplied by the age factor in order to obtain an estimate of expected cases.

The agreement obtained between expected and observed cases is adequate at all ages.

It was observed that in the sample of 175 susceptible children, those who were too young to have onsets at the time of onset of the primary case had later onsets as secondary cases. This is illustrated in Fig. 1, where it may be seen that the age distribution of the sixty-five susceptible children who became later cases is predominantly under 6 years

TABLE XIV

APPLICATION OF AGE FACTORS TO A SAMPLE OF SUSCEPTIBLE CHILDREN AT SPECIFIC TIMES

AGE ATTACK RATE FACTOR APPLIED AT TIME OF ONSET OF PRIMARY CASE

AGE	NUMBER OF CHILDREN	CHILDREN AVAILABLE		AGE FACTOR	CASES		DIFFERENCE
		TOTAL	CORRECTED*		EXPECTED	OBSERVED	
0	12	175	169.0	0.00	0.00	–	–
1	15	163	155.5	0.02	3.11	2	+1.11
2	19	148	138.5	0.06	8.31	9	−0.69
3	15	129	121.5	0.09	10.94	6	+4.94
4	18	114	105.0	0.15	15.75	13	+2.75
5	28	96	82.0	0.21	17.22	22	−4.78
6	25	68	55.5	0.27	14.98	21	−6.02
7	16	43	35.0	0.29	10.15	13	−2.85
8	7	27	23.5	0.32	7.52	7	+0.52
9	10	20	15.0	0.50	7.50	10	−2.50
10	3	10	8.5	0.58	4.93	2	+2.93
11	4	7	5.0	0.61	3.05	3	+0.05
12	–	3	3.0	0.73	2.19	–	+2.19
13+	3	3	1.5	1.00	1.50	2	−0.50
Total	175				107.15	110	

*The children leaving the study at any year of age were present for only one-half the year, on the average. The total of available children has accordingly been reduced by one-half of the life experience of the children leaving in each year.

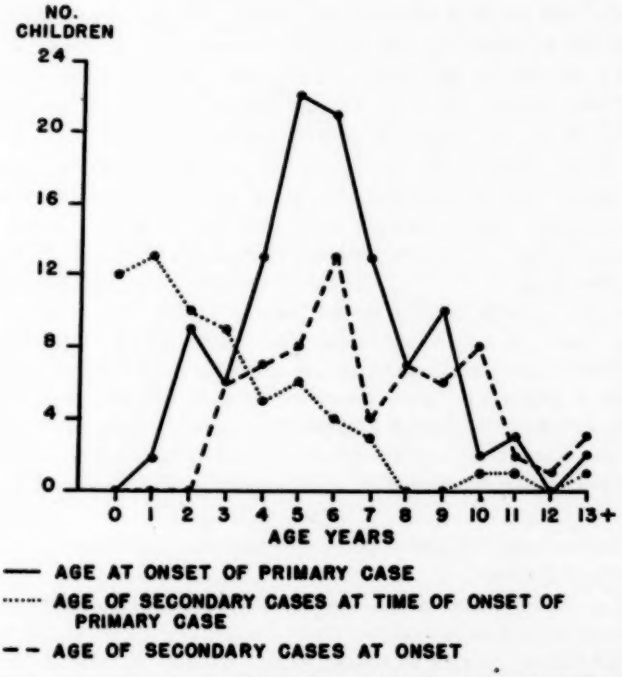

Fig. 1.—The ages of proved susceptible children at the time of onset of the primary case and at onset.

of age at the time of onset of the primary case. The age distribution of the primary cases at onset and the secondary cases at onset is similar and represents the usual onset pattern of rheumatic fever. It is significant that the primary cases in the sample were adequately estimated by the use of the age attack rate factor. It may therefore be concluded that this procedure permits an estimation of the age risk for a series of susceptible children.

Comment

In view of the difficulties encountered in the recognition of the onset of rheumatic fever, the standard sample may not represent an absolutely accurate distribution of case onsets, but it is probably the best that could be expected in a series of children not all of whom had been observed from birth.

It has been demonstrated that the age factors derived from a standard sample are applicable to a suitable series of children known to be susceptible and are adequate to describe the incidence of case onsets in such a sample at any specified time.

The methods described for estimating age expectancy in childhood are precise ones. When all ages are equally represented, it is possible to use the mean age of the sample to estimate total case incidence at any specific time. This method lacks precision, however, and cannot be used in more detailed analyses.

Partial age corrections may be made by excluding part of the data. In rheumatic fever, for example, knowing that the peak age of onset occurs at 6 years, analyses could include only those children who had passed this age. This has the serious disadvantage of excluding a significant portion of the data. Another possibility is to include the children ranging in age from 3 to 9 years. Although not all younger children are eliminated by this method, it does not make an adequate correction for those that are included. Both of these methods were applied to our data and were found to be inadequate.

The age factors which were derived from a series of cases are not applicable per se to a sample containing susceptible and insusceptible children. In such a mixed sample it is first necessary to identify the susceptible children. There is no cutaneous or serologic test to identify the child susceptible to rheumatic fever. However, the genetic studies have demonstrated that the total number of genetically susceptible children in each family may be estimated. Since the age-susceptible children may also be predicted, it now becomes possible to correct this genetic estimate for age by the use of the age factors described.

THE ADEQUACY OF AGE AND GENETIC FACTORS TO DESCRIBE THE INTRAFAMILIAL PATTERN IN RHEUMATIC FEVER

It has been demonstrated that in rheumatic families selected with a bias of at least one affected member per family it is possible to estimate

the total number of cases expected in the sample by appropriate genetic methods. Furthermore, the number of genetic susceptible children present in the families could be estimated at any time during their life experience before they had an opportunity to become affected. It was also shown that each child could be treated separately with reference to his chance genetic susceptibility. Age factors were derived which proved adequate to estimate the number of cases which occurred in a group of known susceptible children at any time during their life experience.

In the following studies, the age and genetic factors described were used in *combination* to estimate the number of cases expected at any time in the life experience of a group of rheumatic families whose offspring included rheumatic and nonrheumatic children. In order to determine whether these techniques were applicable to a mixed sample, a preliminary analysis was made in six arbitrary calendar years. In Table XV it may be seen that by the simultaneous application of age and genetic factors, adequate agreement was obtained between prediction and observation in each year.

TABLE XV*

CASES PREDICTED IN SIX CALENDAR YEARS COMPARED WITH CURRENT OBSERVATION

CALENDAR YEAR	SIBLINGS AVAILABLE	MEAN AGE OF SUSCEPTIBLE SIBLINGS	CASES EXPECTED (CORRECTED FOR AGE)†	CURRENT OBSERVATION‡
		Both Parents Negative		
1924	149	4.0	18.5	16
1927	195	5.4	39.3	37
1930	223	7.2	61.2	64
1933	242	9.3	81.2	85
1936	251	11.2	88.1	97
1939	251	12.2	89.9	101
		One Parent Positive		
1924	113	4.9	28.2	24
1927	151	5.7	46.4	43
1930	176	7.0	70.4	68
1933	193	9.0	95.8	92
1936	203	10.8	107.8	114
1939	205	11.9	110.9	117

*Data from Table VI.

†Genetic expectation was made using the Lenz formula on all families which included at least one eventual case at the time of analysis. The cumulated age factor was applied as a mean age correction to the final expectancy.

‡Cases include only those who had onsets by the specific calendar year in the group of siblings present in that calendar year.

It has been previously demonstrated in the genetic studies that when estimates of the genetic susceptible children present in the families in six calendar years were made, expectation was greater than observation in the earlier calendar years (Table VI). That the susceptible children present in the earlier calendar years had their onsets in later calendar years is shown by the agreement between the total cases expected and the cases finally observed (Table VI).

It will be noted that the mean age of children who eventually became rheumatic was younger in earlier calendar years (Table XV). When the cumulated age

incidence factor was applied to the total genetic expectancy in each calendar year as a *mean age correction*, good agreement was obtained between the corrected expectation and current observation.

The Use of Age and Genetic Factors to Predict the Annual Incidence of Cases

Analysis of the annual incidence of cases frequently reveals the influence of exogenous factors in the spread of disease. It therefore seemed desirable to determine to what extent age and genetic factors would account for the annual incidence of cases in our series of families. By using age and genetic factors in combination, the annual incidence of cases over a twenty-year period, from 1920 to 1939, was predicted. The general procedure was to assign to each sibling in the family an equal individual genetic prediction based on the Lenz formula which was further corrected for age, using the cumulated age incidence factor. Good agreement was obtained between annual expectancy and observation in each year (Table XVI).

TABLE XVI

ANNUAL INCIDENCE OF OBSERVED AND EXPECTED* ONSETS OF RHEUMATIC FEVER IN 102† FAMILIES

CALENDAR YEAR	NUMBER OF NEW FAMILIES	NUMBER OF NEW CHILDREN	CASES EXPECTED	CASES OBSERVED
1920	9	33	7.37	5
1921	6	23	5.76	6
1922	6	22	5.49	6
1923	1	4	2.13	5
1924	8	27	5.05	10
1925	8	26	7.34	7
1926	9	33	10.65	14
1927	16	63	18.32	18
1928	7	39	13.41	22
1929	3	17	10.06	12
1930	3	21	10.51	14
1931	6	32	14.18	16
1932	13	54	19.32	16
1933	6	32	13.78	18
1934	1	7	8.54	16
1935	–	5	6.82	11
1936	–	9	7.10	7
1937	–	1	5.69	5
1938	–	0	5.01	2
1939	–	1	4.23	–

*Genetic expectation was made using the Lenz formula and corrected for age (cumulated age factors), giving a cumulated prediction for each year which includes the estimated values for preceding years. The *annual* prediction for each year is the difference between the cumulated prediction for the current year and the year preceding it.

†Seven families having only one child were omitted.

The families were separated according to genotype and final family size. All children present were entered at the time the family first came under observation in the clinic. Children born after first observation of the family were entered at birth. A separate entry was made for each child in every year from first observation until 1939.

Since a varying number of families entered the clinic each year, each child was entered in the year his family first came under observation rather than at birth,

although it is recognized that he had an age and genetic risk from the time he was born. In a sample in which equal numbers of new families are added each year, this sampling problem does not occur, since the new children entering the study are compensated for by the number of children who reach the age of 13 each year. This situation rarely occurs in clinical data.

Each sibling was given his individual genetic expectancy which was corrected for age by the application of the cumulated age incidence factor. Therefore, in every year each child had a cumulated genetic expectancy corrected for age which increased with each year of life. The expectancies for families where both parents were negative and where one parent was positive were combined, giving a total, age-corrected, cumulated expectancy for every calendar year which could be compared with the observations which were combined in the same way.

In order to determine how many new cases should have been expected in each calender year, the cumulated value for the year preceding was subtracted from the cumulated value for the current year, giving the annual expectancy. Case onsets were recorded from the year in which they were first observed, and the annual incidence of observed cases was derived similarly.

It will be noted that in the years 1927 and 1932 a greater number of families entered the study. This is reflected in higher expectancies and observations obtained in these years and the two years immediately succeeding them. Since every new family which came under observation had at least one sibling case, these observed increases may be attributed to sampling.

These observations indicate that in every year the estimated number of susceptible children present in the families who *were of a susceptible age developed rheumatic fever.* It is of epidemiologic significance that during the twenty-year period of observation, the annual rate of prevalence of rheumatic fever was adequately defined by age and genetic factors. That is, at no period was there a significantly greater prevalence of the disease than was expected on an age and genetic basis.

It is of interest that analysis of the *seasonal* prevalence of onsets in 113 children for whom the month of onset was accurately recorded showed a *comparable* increased rate of prevalence in every spring season for each calendar year. However, in two calendar years the rate of prevalence in the winter and summer exceeded that in the spring season. This observation confirms the clinical impression that when the weather is unseasonable, an increase in rheumatic fever is apt to occur.

The Use of Age and Genetic Factors for Predictions at the Time of Onset and Subsequent to the Onset of the Primary Case

Some observers have suggested on the basis of epidemiologic analysis that the primary case in the family constitutes a risk for other members of the household. In these studies the individual age and genetic risks were not evaluated.[10, 11]

It has already been demonstrated in the genetic studies that at the time of onset of the primary case the predicted number of susceptible children in the sample was eventually realized as cases. A comparison of the ages of affected and unaffected *among known susceptible children* present in the families at the time of onset of the primary case revealed

that the mean age of the affected children was about 6 years while that of the unaffected was from 2 to 3 years (Table XVII). It is to be emphasized that the *ages of onset* of primary and secondary cases were comparable (Fig. 1). This indicates that the susceptible children who were not realized as cases at the time of onset of the primary case were not of a susceptible age. In the period following the onset of the primary case, most of the susceptible children were of a susceptible age. Since the epidemiologic analysis at the time of onset and subsequent to the onset of the primary case in the families involved differences in technique, a separate consideration of the methodology is necessary.

TABLE XVII

COMPARISON OF MEAN AGES OF PRIMARY AND SECONDARY CASES

	SIBLINGS AVAILABLE	CASES EXPECTED	PRIMARY CASES		SECONDARY CASES PRESENT AT ONSET OF PRIMARY CASE		
			OBSERVED	MEAN AGE AT ONSET	OBSERVED	MEAN AGE	
						CURRENT	AT ONSET
A. At the Time of Onset of Primary Case							
Both parents negative	190	78.5	60	5.9	23	2.3	6.8
One parent positive	152	88.7	50	5.7	42	3.2	7.0

	SIBLINGS* AVAILABLE	CASES EXPECTED	CASES OBSERVED	MEAN AGE	
				AT ONSET	1939
B. After the Onset of Primary Case (1939)					
Both parents negative	191	47.8	41	6.1	11.5
One parent positive	155	77.5	67	6.6	11.5

*Includes all siblings present in the families in 1939 except the primary cases.

Predictions at the Time of Onset of the Primary Case

At the time of onset of the first case, there is only one known case in every family by definition. Obviously, these cases occur in the families in different calendar years, and the first case will occur when at least one genetically susceptible child has, on the average, reached the age of 6 years, regardless of the ages of the other members of the family. The children who have passed the peak age of onset are probably not genetically susceptible, or they would already have been affected, and the children under the peak age of onset are, in general, too young to be affected, even though some of them may well be genetically susceptible. It may be postulated that the probability that any child will be the first affected sibling in his family is defined by the age incidence factor, which states that 2 per cent of all cases occur at the age of 1 year, 15 per cent of all cases occur at the age of 6 years, and 1 per cent occur at the age of 12 years (Table XI, A).

TABLE XVIII

CASES EXPECTED AND OBSERVED AT THE TIME OF ONSET OF THE PRIMARY CASE

AGE	SIBLINGS AVAILABLE	AGE FACTOR	AGE PROBABILITY	RELATIVE AGE PROBABILITY	ADJUSTED TOTAL EXPECTANCY (78.5)	SUSCEPTIBLE CHILDREN AVAILABLE		AGE ATTACK RATE	CASES	
						TOTAL	CORRECTED		EXPECTED	OBSERVED
Both Parents Negative										
0	7	0.00	0.00	0.00	–	78.50	78.50	0.00	–	–
1	16	0.02	0.32	0.02	1.57	78.50	77.72	0.02	1.55	1
2	14	0.06	0.84	0.06	4.71	76.93	74.57	0.06	4.47	4
3	15	0.09	1.35	0.09	7.06	72.22	68.69	0.09	6.18	3
4	11	0.13	1.43	0.09	7.06	65.16	61.63	0.15	9.24	5
5	18	0.15	2.70	0.18	14.13	58.10	51.04	0.21	10.72	14
6	23	0.15	3.45	0.23	18.06	43.97	34.94	0.27	9.43	16
7	14	0.12	1.68	0.11	8.64	25.91	21.59	0.29	6.26	4
8	10	0.09	0.90	0.06	4.71	17.27	14.91	0.32	4.77	3
9	18	0.10	1.80	0.12	9.42	12.56	7.85	0.50	3.92	6
10	8	0.06	0.48	0.03	2.36	3.14	1.96	0.58	1.14	1
11	10	0.02	0.20	0.01	0.78	0.78	0.39	0.61	0.24	2
12	6	0.01	0.06	0.00	–	–	–	0.73	–	–
13+	20	0.00	0.00	0.00	–	–	–	1.00	–	1
Total	190		15.21						57.92	60
One Parent Positive										
					(88.7)					
0	10	0.00	0.00	0.00	–	87.81	87.81	0.00	–	–
1	10	0.02	0.20	0.02	1.77	87.81	86.93	0.02	1.74	1
2	19	0.06	1.14	0.09	7.98	86.04	82.05	0.06	4.92	5
3	12	0.09	1.08	0.08	7.10	78.06	74.51	0.09	6.70	3
4	14	0.13	1.82	0.14	12.42	70.96	64.75	0.15	9.71	8
5	19	0.15	2.85	0.22	19.51	58.54	48.78	0.21	10.24	8
6	14	0.15	2.10	0.16	14.19	39.03	31.93	0.27	8.62	5
7	15	0.12	1.80	0.14	12.42	24.84	18.63	0.29	5.40	9
8	5	0.09	0.45	0.04	3.55	12.42	10.64	0.32	3.40	4
9	9	0.10	0.90	0.07	6.21	8.87	5.77	0.50	2.88	4
10	4	0.06	0.24	0.02	1.77	2.66	1.78	0.58	1.03	1
11	9	0.02	0.18	0.01	0.89	0.89	0.45	0.61	0.27	1
12	1	0.01	0.01	0.00	–	–	–	0.73	–	–
13+	11	0.00	0.00	0.00	–	–	–	1.00	–	1
Total	152		12.77						54.91	50

For example, in a family of three children aged 12, 6, and 3 years, respectively, at the time of onset of the first case the 12-year-old child would have been affected already if he were genetically susceptible (his current risk in terms of the standard age incidence factor is 1 per cent); the 3-year-old, even though he may be genetically susceptible, has a current age risk of 9 per cent; while the 6-year-old has the greatest likelihood of being affected if he is genetically susceptible, since his current age risk is 15 per cent. The total risk for these three children is 25 (that is, 15 + 9 + 1). Of these it is apparent that on the average the 6-year-old child has a 60 per cent relative chance of being the primary case as compared to the 12-year-old child who has a 4 per cent chance or the 3-year-old child who has a 36 per cent chance, provided that all are genetically susceptible.

It is not analytically possible to identify the individual child who is genetically susceptible, although the total number of genetically susceptible children present in a family may be estimated from the Lenz formula. Since the chance that any one of these predicted susceptible children will be the primary case is a function of his current age, the total genetic estimate may be apportioned as a series of individual expectancies among the siblings present in accordance with their age probability. It is apparent that an unequal individual genetic expectancy has been postulated. By this procedure the probable number of *genetically susceptible children* present in the sample at each age was ascertained (Table XVIII). The number of these susceptible children who would be expected to be primary cases was predicted by application of the age attack rate factor. In Table XVIII it may be seen that expectation of primary cases was adequately realized at every age in both the negative and positive parent families. It may therefore be concluded that it is possible to predict the onset of primary cases on an age and genetic basis.

It is important to note that the use of the Lenz formula in this procedure obviates any selective bias due to the inclusion of the index case. The genetic and age aspects of the computation have been supported by other evidence. One further assumption has been made; namely, that the probability that any child will be a first case in his family is defined by the age incidence factor. The agreement obtained between expectation and observation indicates that the method used is adequate for the prediction of primary cases. The details of the methodology used in this analysis are illustrated in Table XIX.

In Table XIX, A, the details of this procedure are illustrated for three families. It will be noted that each child is given an age probability based on his current age, using the age incidence factor. The *relative* age probability on the basis of 100 per cent is then determined for each child. This is applied to the total genetic expectancy for the family, giving a relative age-genetic expectancy for each child.

In the analysis of the entire sample a similar procedure was followed. Since the number of genetic susceptible children present in the families had already been found to be 78.5, it was not necessary to treat each family separately, and the entire sample was treated as one family. The relative age probability for the entire sample depends on the relative number of children available at each age. Consequently, the age incidence factor was applied directly to the entire sample grouped according to age at the time of onset of the primary case, and the relative age probability on the basis of 100 per cent was determined. The validity of this procedure becomes apparent when it is recognized that at the time of onset of the primary case the age constitution of all of the families was similar. This was substantiated by treating a representative sample of the data as separate families and as one family, and it was found that identical results were obtained.

At the time of onset of the first case, the risk for any susceptible child to become affected in the current year is given by the age attack rate factor. The genetic susceptible children defined above were tabulated according to the number who *reached each age* by the time of onset of the primary case (Table XVIII, B). A one-half year correction was introduced on the assumption that a group of children

TABLE XIX

PROCEDURE FOR PREDICTING THE NUMBER OF CASES EXPECTED AT THE TIME OF ONSET OF THE FIRST CASE IN THREE FAMILIES

I. Distribution of Total Genetic Expectancy According to Age

	FAMILY A			FAMILY B			FAMILY C		
	S_1	S_2	S_3	S_1	S_2	S_3	S_1	S_2	S_3
1. Age of siblings at time of onset of the first case	6	4	2	10	9	6	5	1	0
2. Age chance of being the first case (%)*	15	13	6	6	10	15	15	2	0
3. Total age chance for family	←	34	→	←	31	→	←	17	→
4. Per cent of total age chance at specified age	44	38	18	19	32	48	88	12	0
5. Total genetic expectancy for family†		1.297			1.297			1.297	
6. Age genetic chance for each sibling [(4) × (5)]	0.57	0.49	0.23	0.25	0.42	0.62	1.14	0.16	0

II. Prediction of Number of Primary Cases Expected in Three Families

SIBLINGS		AGE GENETIC CHANCE (6)	TOTAL AGE GENETIC CHANCE AT EACH AGE		AGE ATTACK RATE FACTOR	CASES		
						EXPECTED		OBSERVED
AGE	NUMBER		TOTAL	CORRECTED‡		TOTAL	CORRECTED‡	
0	1	0.00	3.88	3.88	0.00	0.00	0.00	
1	1	0.16	3.88	3.80	0.02	0.08	0.08	
2	1	0.23	3.72	3.60	0.06	0.22	0.22	1
3	–	–	3.49	3.49	0.09	0.31	0.31	
4	1	0.49	3.49	3.25	0.15	0.52	0.50	
5	1	1.14	3.00	2.43	0.21	0.63	0.51	1
6	2	1.19	1.86	1.26	0.27	0.50	0.34	1
7	–	–	0.67	0.67	0.29	0.19	0.19	
8	–	–	0.67	0.67	0.32	0.21	0.21	
9	1	0.42	0.67	0.46	0.50	0.34	0.23	
10	1	0.25	0.25	0.13	0.58	0.14	0.03	
Total	9	3.88				3.14	2.62	3

*Age incidence factor.

†Genetic factor derived from Lenz formula for families with three sibships when both parents are negative.

‡A half-year correction has been introduced (see text).

leaving the study within a year are present for an average of six months. The age attack rate factor was then applied, and the number of predicted cases was compared with observation at each age.

Predictions Subsequent to the Onset of the Primary Case.—The number of cases occurring subsequent to the onset of the primary case in the family was estimated, using simple genetic ratios (0.25 for negative-by-negative and 0.50 for positive-by-negative families, respectively). These values were corrected for age, using the cumulated age incidence factor derived from the standard sample. Since the ages of all children in 1939 were used, and all children were included except the primary case, there were no specific sampling problems, and the direct use of the

age and genetic factors was sufficient to describe the onsets of later cases. In Table XX it may be seen that there is adequate agreement at each age for both groups of families.

It has been demonstrated that primary and secondary cases may be predicted on an age and genetic basis. It would appear that the risk for susceptible children in a rheumatic family to develop rheumatic fever is no greater before or after the onset of the first case in the family. Whatever other factors are responsible for the onset of rheumatic fever, in susceptible children they would seem to be equally operative in both situations.

TABLE XX

CASES PREDICTED AND OBSERVED FOLLOWING THE ONSET OF THE PRIMARY CASE

AGE	BOTH PARENTS NEGATIVE					ONE PARENT POSITIVE				
	SIBLINGS AVAILABLE	TOTAL CASES EXPECTED	AGE FACTOR	CURRENT CASES EXPECTED	CASES OBSERVED	SIBLINGS AVAILABLE	TOTAL CASES EXPECTED	AGE FACTOR	CURRENT CASES EXPECTED	CASES OBSERVED
0			0.00	–		1	0.50	0.00	–	
1			0.02	–		–	–	0.02	–	
2			0.08	–		2	1.00	0.08	0.08	
3	4	1.00	0.17	0.17		6	3.00	0.17	0.51	
4	6	1.50	0.29	0.44		1	0.50	0.29	0.14	
5	3	0.75	0.44	0.33	1	7	3.50	0.44	1.54	1
6	6	1.50	0.59	0.88	1	8	4.00	0.59	2.36	2
7	5	1.25	0.71	0.89	1	4	2.00	0.71	1.42	1
8	11	2.75	0.81	2.23	2	4	2.00	0.81	1.62	3
9	7	1.75	0.90	1.58	2	6	3.00	0.90	2.70	4
10	11	2.75	0.96	2.64	5	13	6.50	0.96	6.24	12
11	10	2.50	0.98	2.45	3	5	2.50	0.98	2.45	1
12	6	1.50	1.00	1.50	–	7	3.50	1.00	3.50	5
13+	122	30.50	1.00	30.50	26	91	45.50	1.00	45.50	38
Total	191	47.75		43.61	41	155	77.50		68.06	67

Comment

Analytic procedures were developed which permitted the statistical estimation of the genetic and age risk for every sibling to be a case at any specified time. In the analyses presented it has been demonstrated that the simultaneous application of age and genetic factors accounted adequately for the incidence of cases observed at various times during the life experience of the families; namely, in any calendar year, at the time of onset of the primary case and subsequent to the onset of the primary case. The intrafamilial pattern of spread of rheumatic fever has been described in numerical terms by the use of age and genetic factors.

It is apparent that in this series of families, genetically susceptible children, whether primary or secondary cases, developed rheumatic fever when they reached a characteristic age. The age risk would appear to be the important factor in determining the time of occurrence of cases in the family.

In these analyses, the age and genetic risks have been treated numerically, without any attempt to interpret the fundamental basis for their expression. It would seem reasonable to consider that the genetic risk is primary, and that the age risk is inherent in the genetic risk; that is, the age risk may reflect relative degrees of genetic susceptibility. However, secondary nongenetic factors may be responsible, the age risk reflecting the interval of time necessary for the development of manifest disease. Whatever interpretation one accepts, it is evident that the age risk is a significant factor in the pattern of spread of the disease.

The adequacy with which age and genetic factors described the annual incidence of cases over a twenty-year period, as well as primary and secondary cases, in this series of families suggests that whatever exogenous factors were operative they were uniformly available.

Of particular epidemiologic significance is the observation that there was no significant difference between expectation and observation at the time of onset of the primary case and subsequently. That is, the first child affected did not constitute any obvious risk to his susceptible siblings.

THE ROLE OF ENVIRONMENTAL FACTORS

Communicability

The concept that the intrafamilial spread of rheumatic fever is due to contact with a rheumatic parent or a sibling during an acute episode or a quiescent phase of the disease did not receive support in our previous epidemiologic studies. Communicability on a short incubation period was excluded, although the possibility of a long incubation period remained. There was no concentration of cases at any particular time interval. Assuming exposure, intimate and casual contact appeared to be equally effective.[12] The adequacy of age and genetic factors to describe the intrafamilial pattern of spread of rheumatic fever in these families is further corroborative evidence for this concept.

The Use of Secondary Attack Rates in Rheumatic Fever.—In the acute communicable diseases, the conventional measure of the degree of communicability is the secondary attack rate (the ratio in per cent of cases to person years of life experience, following exposure to the first case in the family). When a low rate is obtained, the disease is considered to be less communicable than a disease whose rate is higher. Provided that diagnostic criteria and sampling conditions are standardized, every communicable disease has one characteristic secondary attack rate.[36] This epidemiologic procedure has been found suitable for the study of the intrafamilial spread of a chronic disease such as tuberculosis.[39] More recently it has been adopted for the study of the familial association of rheumatic fever.[10, 12]

In Table XVIII of the Appendix it may be seen that in rheumatic fever two secondary attack rates were obtained, that for children in

TABLE XXI

"SECONDARY ATTACK RATES" OF SUSCEPTIBLE CHILDREN IN 105 RHEUMATIC FAMILIES

AGE	CHILDREN EXPOSED	CASES AT ONSET	AVERAGE YEARS OF LIFE EXPERIENCE	SECONDARY ATTACK RATE (%)
Both Parents Negative				
Birth	18	–	–	–
0	3	–	10.5	–
1	8	–	25.0	–
2	4	1	30.5	3.3
3	4	5	31.5	15.9
4	1	8	27.5	29.1
5	1	6	21.5	27.9
6	1	8	15.5	51.6
7	–	–	12.0	–
8	–	3	10.5	28.6
9	–	4	7.0	57.1
10	–	3	3.5	85.7
11	1	2	1.5	133.3
12	–	–	1.0	–
13+	–	1	0.5	200.0
Total	41	41	198.0	20.7
One Parent Positive				
Birth	25	–	–	–
0	9	–	17.0	–
1	5	–	36.5	–
2	6	2	41.0	4.9
3	5	7	42.0	16.7
4	4	4	41.0	9.8
5	5	9	39.0	23.1
6	3	12	32.5	36.9
7	3	10	24.5	40.8
8	–	10	16.0	62.5
9	–	3	9.5	31.6
10	1	5	6.0	83.3
11	–	1	3.5	28.6
12	–	1	2.5	40.0
13+	1	3	1.0	300.0
Total	67	67	312.0	21.5

families where one parent is rheumatic being about twice that for children in families where both parents are negative. Since parental exposure was excluded, these findings may be considered a reflection of the genetic difference between the two groups of families rather than a measure of communicability.[12] It must be emphasized that the separate analysis of the two parental groups does not render the influence of the hereditary factors constant, but only reveals the difference in frequency of susceptible children in the two groups. The individual genetic risk is not considered, for this method assumes that all siblings are equally susceptible.

When secondary attack rates are made in such communicable diseases as measles and diphtheria, immune (insusceptible) members of the household are excluded from the analysis. On the assumption that only genetically susceptible individuals develop rheumatic fever, age-specific secondary attack rates were made using only the life experience of children who eventually became affected (proved to be susceptible). This

is consistent with the observation in the genetic studies that apparently all the genetically susceptible children predicted in these families became affected. The elimination of all negative (insusceptible) children had the effect of removing the genetic disproportion between affected and unaffected children in the two groups of families. The rates obtained for the two parental groups, using the primary case as the source of exposure, were found to be the same for both groups of families (Table XXI). Elimination of the presumed insusceptible children equalized the rates.

The high rate obtained (22 per cent) might erroneously be considered an indication of the risk of familial association, and it would then appear that rheumatic fever is highly contagious. However, this analysis may better be regarded as a reflection of the age specificity of the disease in a group of individuals, 100 per cent of whom were attacked.

That this "rate" had little bearing on intrafamilial association may be inferred from the fact that the same observations could be derived from any independent sample of cases, regardless of whether they were brothers and sisters, simply by computing their life experience through their year of onset and making a "rate."

The use of rates for the study of familial association in rheumatic fever is limited by the fact that the individual children who are susceptible cannot be identified. If the life experience of all siblings is included, genetic differences are not accounted for. If the life experience of proved susceptible children alone is included, the possibility remains that susceptible children who might eventually become affected are also excluded. These observations indicate that secondary attack rates are not adequate to study familial association in rheumatic fever.

Risk Prior and Subsequent to the Onset of a Case.—A comparison of the life experience prior and subsequent to the onset of a case in the family has been proposed as a method for determining whether association with an affected member constitutes a hazard to other members of the household.[10, 11] This technical procedure is subject to the same reservations that are encountered in using secondary attack rates in rheumatic fever.

Furthermore, in this type of analysis two conflicting results may be obtained, depending on the treatment of the index case. Due to the age expression of rheumatic fever, the index case is usually a primary case. When the index case is excluded from the analysis, an apparently greater risk following association with the primary case is obtained.[10, 11] If no correction is made for the index case, there is no difference in risk.[12, 40]

It has already been demonstrated that age and genetic factors are adequate to account for the incidence of cases in rheumatic families at the time of onset and subsequent to the onset of the primary case. In this analysis, the bias due to the inclusion of the index case was corrected for numerically. The observation that all genetically susceptible

children of a susceptible age were realized as cases at the time of onset of the primary case and subsequently would seem to indicate that the risk was equal in both periods.

If the acquisition of rheumatic fever by a susceptible child follows exposure to a rheumatic individual, these observations indicate that casual and intimate exposure are equally effective. Since a short incubation period was excluded, a variable incubation period from one to ten years, averaging six years, would have to be postulated on any theory of communicability.

Economic Status

Rheumatic fever is considered to be more prevalent among underprivileged children than among those of the well-to-do, although conclusive factual information for comparison is not available.

Our data, which are limited to a clinic population in New York City, do not permit a complete evaluation of the role of environment, that is, living conditions, in rheumatic fever. However, it was possible to compare the relative influence of certain unfavorable environmental factors in our families. In addition, it was essential to determine whether internal differences due to environment were present, or whether, for purposes of analysis, the data might be grouped without regard for the recorded environmental differences.

On the assumption that only genetically susceptible children develop rheumatic fever, the data were analyzed, using age and genetic factors to determine whether case incidence would be lower than expectation in the families living under relatively favorable environmental conditions.

Analyses of the 109 families subdivided into four environmental groups were made (Table XXII).

Group I: Relatively favorable environment and adequate diet
Group II: Opportunity for chilling
Group III: Inadequate diet
Group IV: Opportunity for chilling and inadequate diet

The total genetic expectations show that in each environmental group the number of cases expected were fully realized, except for Group IV, where there was an excess of cases. There was, however, no regular trend between the number of cases realized in the relatively good environment and in the more unfavorable environments. The difference between Group I and Group IV was not found to be significant.

In previous studies it has been shown that the children in Group IV were slightly younger than the others.[12] In order to determine whether or not this difference in age would make apparent a greater difference in the agreement of expected and observed cases, the predictions were corrected on an age-specific basis, using the cumulated age incidence

TABLE XXII

GENETIC PREDICTIONS IN FOUR ENVIRONMENTAL GROUPS (1939)*

	BOTH PARENTS NEGATIVE					ONE PARENT POSITIVE				
	NUMBER OF FAMILIES	NUMBER OF CHILDREN	CASES			NUMBER OF FAMILIES	NUMBER OF CHILDREN	CASES		
			EXPECTED†		OBSERVED			EXPECTED†		OBSERVED
			TOTAL	AGE CORRECTED				TOTAL	AGE CORRECTED	
Group I	17	72	25.80	24.44	28	18	64	36.02	34.25	39
Group II	8	29	11.44	10.30	13	6	18	10.52	10.16	10
Group III	18	79	27.79	26.17	29	14	63	33.87	28.85	27
Group IV	16	71	24.88	23.17	31	12	60	31.63	27.96	41

*Group I: Relatively favorable environment, adequate diet.
Group II: Opportunity for chilling.
Group III: Food insufficient in quantity and poorly balanced.
Group IV: Opportunity for chilling, insufficient food, poor maternal care.
†Predictions were made using the Lenz formula. Corrections for age were made using the cumulated age factor, age specifically.

factor. Although predictions were reduced in both Groups I and IV by this method, the differences between the two groups were not significant.

The possibility that sampling might account for the small differences in the two groups was investigated. This would be true if there were a greater proportion of multiple case families in Group IV than would be expected in a random sample. It was found that the mean family size was four in both Groups I and IV in the negative parent families and in Group I in the positive parent families. In Group IV of the positive parent families the mean family size was five. Since the entire sample had a mean family size of four children, this finding demonstrates a small and inconclusive difference. In the negative parent families, one family out of seventeen had three or more cases in Group I, while six out of sixteen families in Group IV had three or more cases. In the positive parent families, five families out of eighteen had three or more cases in Group I, while in Group IV, seven out of twelve families had multiple cases. These are small differences which are not conclusive. The trend indicates that sampling may account for the higher incidence of cases in Group IV.

Within the limits of the environmental conditions studied, no significant difference in the incidence of cases among susceptible individuals was observed between the most and least favorable groups studied. If living conditions are important factors in the prevalence of the disease, the range in our data between the best and worst environments was too narrow for a difference to be demonstrable.

The influence of environment cannot be fully evaluated until similar studies are made among the well to do and in families living in geographic localities where the prevalence of the disease is reported to be low.

It is possible that the numerical difference in incidence between underprivileged families and families of the well to do in the general population is so marked that the increased prevalence of rheumatic fever among underprivileged children may be more apparent than real. The impression that rheumatic fever is more prevalent among the underprivileged may also be due to a difference in severity, rather than incidence, so that a relatively mild form of the disease occurring among the well to do might be unrecognized. It is also possible that the disease is less severe in localities where the disease is reported to be uncommon.

It must be emphasized that these studies do not include a complete analysis of the role of environment but are sharply limited to a specific group of data in which environment (living conditions) has been treated in general terms. It is possible that more specific dietary studies in these rheumatic families may have revealed differences in vitamin consumption or requirements.[41]

RÉSUMÉ

Modern Genetic Theory

The study of human heredity as a medical subject is a relatively new field. In the past there have been a number of purely genetic studies on rare conditions, but to our knowledge no systematic analysis of the

interaction of genetic and exogenous factors has been presented for any human disease. Although the application of genetic techniques to human material involves certain difficulties, it is not, for the most part, beyond clinical medicine. The reasoning is simple and the arithmetic details are easy to follow and apply.

Many conditions appear to "run in families," and the observed familial incidence cannot be considered as conclusive evidence for heredity. The attempt to link heredity with familial incidence has been associated with the concept of constitution, which embraces a variety of poorly defined traits. Modern genetic theory refers to explicit cellular and functional attributes and properties whose precursors have a concrete and real existence in the germ cells and the soma.

Fundamentally, all statements about heredity refer to the chromosomes upon which the genes are located. Variations in the mechanism of heredity depend on processes associated with the maturation of the germ cells and the fertilized egg. Inasmuch as all hereditary characters probably depend upon the effect of a variety of exogenous factors for their somatic expression, hereditary traits may be variable in the time and degree of their expression. Not infrequently they may fail to be expressed altogether, even though the host may be genetically susceptible. It is therefore essential to evaluate the effect of nongenetic factors, environmental, dietary, or bacterial.

In the study of any hereditary condition, the pattern of inheritance is described in terms of some one of the known mechanisms of inheritance in man. By the use of appropriate formulas which have been derived on the basis of experimental studies, the theoretical distribution of susceptible individuals in a series of human families is made and compared with the actual observation for each family size. If agreement is obtained, the data are considered to be consistent with the hypothesis postulated. Consistency with a postulated mechanism is not in itself proof. Other mechanisms of heredity must be excluded. Significant differences between observation and expectation negate the mechanism postulated. Consistent deficiencies or excesses of cases may indicate nongenetic effects if bias in the data is excluded. For these reasons the requirements of the data suitable for the application of genetic formulas are one of the most important aspects of the genetic analysis. The bias introduced and the errors of interpretation arising from a lack of recognition of these requirements in rheumatic fever data have been fully discussed.

Methods of Genetic Analysis

The presentation of the genetic procedures of analysis has been given in great detail to permit comparable studies not only for rheumatic fever, but also for other diseases in which the factor of heredity is to be investigated.

It may be noted in passing that in medical literature there is not generally available a study illustrating the use of existing genetic formulas for the genetic analysis of disease in man. In these studies, the use of available genetic formulas was presented as simply as possible. In some instances formulas were extended for purposes of epidemiologic analysis.

Various methods of genetic analysis have been presented. Of these the Lenz-Hogben formula for estimating case frequency in data biased by the inclusion of at least one sibling case has been given particular emphasis because of the facility of its application. Other formulas have been presented which are equally applicable to the data of rheumatic fever. These have been used in our studies for obtaining corroborative evidence for the genetic mechanism postulated.

Alternative mechanisms of heredity were for the most part excluded; namely, simple dominance, sex linkage, and complementary recessive and complementary dominant inheritance. Further corroborative evidence was obtained by the analysis of a comparable small series from another clinic. Probably the best proof of the hereditary mechanism which was postulated would be available from an analysis of families selected because one or both parents were rheumatic. Such data are now being collected for analysis. Analytic procedures have been applied to many subdivisions of the data, and in every instance confirmatory evidence was obtained.

On the basis of the studies presented, single autosomal recessive inheritance in rheumatic fever was postulated. It is to be emphasized that once a hereditary mechanism has been established, procedures for genetic analysis are simplified. They consist in applying the appropriate formula to the data in order to obtain the theoretical incidence of cases which may be compared to the actual number of cases observed.

Extensions of the Genetic Analysis

In classical genetic analysis, a theoretical *average* estimate of case incidence is established for each family size. Using this statistical estimate, the *final* number of cases in a group of families may be predicted. When such a prediction is made *before* all of the members have had an opportunity to become affected, the prediction represents an average estimate of the number of susceptible individuals present in the sample at the time of analysis. It has been shown in these studies that the number of susceptible individuals present in the families can be predicted at any time, even before they have had an opportunity to be cases. Predictions made in early calendar years (e.g., 1924) were fully realized in later calendar years (e.g., 1939). In other words, the genetic risk for a group of families may be stated in numerical terms, and the genetic risk for an individual family may be stated similarly.

Within a family the genetic risk for each sibling may be evaluated, although the individual siblings who are susceptible cannot be identified.

It has been shown that the average estimate for the family may be divided equally among all siblings, if the genetic variable alone is considered or apportioned unequally with respect to another variable. Although these numerical expressions do not measure degrees of real genetic susceptibility among siblings, nor do they differentiate between susceptible and insusceptible individuals, they provide a means of expressing the intrafamilial genetic risk.

Age Expression of Rheumatic Fever

The age risk in rheumatic fever is probably one of the most important factors in the evolution of the disease. It is obvious that the risk of attack for a 1-year-old child is not as great as the risk for a 6-year-old child. The interpretation of age susceptibility in rheumatic fever is dependent upon the etiologic concept of the disease which is postulated. It is conceivable that the age risk is on a genetic basis alone, but it is more likely that nongenetic factors are contributory.

In order to express the dynamic sequence of events in these families, a numerical expression of the age incidence of the disease was derived from an independent sample of 688 rheumatic children which was representative and sufficiently accurate. In these analyses, the upper age limit was considered to be 13 years. It is our opinion that onsets in adult life are probably not of sufficient frequency to invalidate our observations. Three standard expressions of case incidence were established: case incidence *at* specific ages, cumulated case incidence *by* any specific age, and the age attack rate. These age factors are applicable only to a group of susceptible children. The use of any particular age factor was shown to be dependent upon the character of the sample of susceptible children to which it was applied and the kind of information which was desired. The use of age factors in our studies was demonstrated in the combined genetic and epidemiologic analyses.

Adequacy of Age and Genetic Factors to Describe the Familial Pattern of Spread of Rheumatic Fever

The development of statistical equivalents for individual genetic risk and numerical measures of the age risk made it possible to describe the case incidence in our families under various conditions in numerical terms. It was shown that age and genetic factors described the pattern of intrafamilial spread of the disease at any time during the life experience of our families. Using age and genetic factors, the annual incidence of cases during a twenty-year period was predicted. Of particular epidemiologic significance is the agreement which was found between prediction and observation at the time of onset of the primary case and subsequently.

Although these observations do not exclude the operation of other exciting factors which may be responsible for the *onset* of the disease in susceptible children, they do indicate that whatever these factors

are, they are uniformly operative at all times during the life experience of the families. Although it was apparent that the average number of genetically susceptible children predicted in these families was finally realized, it cannot be concluded that every genetically susceptible child in the general population will *necessarily* develop rheumatic fever.

The integration of genetic and epidemiologic methods of analysis is an approach hitherto not formulated for any disease. Its usefulness in these studies warrants their extension to other comparable problems of investigation.

Epidemiologic Analysis

Epidemiologic analysis did not lend support to the concept that the spread of the disease resulted from contact with an active or inactive rheumatic member. There was no concentration of cases at any time interval. Of particular importance is the observation that the ages of onset of primary and secondary cases were similar. This excludes communicability on a short incubation period hypothesis. It was shown that in rheumatic fever, secondary attack rates reflected the genetic and age characteristics of the disease. All of these observations indicate that rheumatic fever does not exhibit the usual characteristics of a communicable disease.

The limitation of our data to a sample from a clinic population in New York City prevented a full evaluation of the influence of environment (living conditions) in the development of the disease. There was no significant difference in the incidence of onsets of rheumatic fever among susceptible children in relatively favorable and unfavorable environmental groups studied. It is probable that a common component, dietary or otherwise, was operative. Comparable analyses among families of the well-to-do and in different geographic locations are necessary before the influence of environment in rheumatic fever can be fully evaluated.

Philosophic Considerations of the Nature of Rheumatic Fever

In a lucid consideration of general principles of epidemiologic procedure, Frost states the following:

> In collecting facts about the distribution of disease, the purpose in view is always to a better understanding of its nature, sources, means of spread and eventually of its control. This implies that the facts must be related to each other in such an orderly way as to establish a theory or philosophy of the disease. . . . Given sufficient scope and accuracy of observation, a conclusion as to the nature and spread of a disease may often be established quite firmly by circumstantial evidence well in advance of experimental observation. Moreover, many problems of disease transmission which are highly important from the standpoint of prevention are such that can be solved only by investigation of this kind. The weakness in conclusions drawn from circumstantial studies is usually chargeable not to basic defects in the methods of investigation but more often to paucity or inaccuracy of data, or to faults of logic in their interpretation.[36]

This approach is particularly applicable to the study of an obscure disease such as rheumatic fever. It has yielded observations which permit a rational description of the disease as it affects attacked families.

It has been shown that in families selected because of the presence of at least one rheumatic child, the distribution of cases follows the general laws of inheritance. It was also observed that the frequency of cases is consistent with the hereditary mechanism of a single autosomal recessive gene. Predictions based on the hereditary mechanism postulated were finally realized. It may therefore be concluded that susceptibility to rheumatic fever is hereditary. Since these genetic predictions represent average estimates of the number of genetic susceptible individuals present in the families studied, it may also be stated that *in these families* all genetically susceptible children developed rheumatic fever. Accepting susceptibility of the host to be on a genetic basis, nonrheumatic siblings in the family may be considered insusceptible.

In these studies, genetic susceptible individuals expressed the disease during a characteristic age period; that is, at a susceptible age. It was found that when the age risk was taken into account, the frequency of *onsets* could be estimated at any time in the life experience of the susceptible children in the families studied. Age and genetic factors were adequate to describe the intrafamilial pattern of spread for onsets of the disease at specific calender years over a period of twenty years, at epidemiologic points of analysis, and among families of certain environmental groups.

Rheumatic fever was not found to exhibit the usual characteristics of a communicable disease. The observations are not consistent with the operation of any specific bacterial agent. No evidence was obtained to support the postulate that contact with an active or quiescent rheumatic individual was responsible for the *onset* of the disease in susceptible children. In this sense, the hemolytic streptococcus would be no more likely than any other specific microorganism. If bacterial agents are responsible for the onset of rheumatic fever, our observations indicate that they would appear to be ubiquitous. The possible role of other environmental factors such as climatic or dietary factors was not entirely excluded. If operative, these were apparently uniformly available or effective. Recent studies have suggested that differences in vitamin requirements may be on a genetic basis. This aspect of the problem is under investigation.

On the basis of the data which have been presented, specific statements as to the etiology of rheumatic fever and its control cannot be made. The evidence which has been obtained is obviously limited to families selected from children attending a clinic in New York City. Comparable observations would be expected and have been obtained in a similar urban clinic population in another city. Should further

studies of families in different geographic and economic environments reveal a difference in penetrance of the disease, methods for the control of rheumatic fever would be available. Such data are now being collected.

If these observations are valid, it would appear reasonable to postulate that distributed in the general population there are children who are susceptible or insusceptible to rheumatic fever on a genetic basis.

One may speculate that in a genetically susceptible child, the connective tissue system, by reason of inherent anatomic or physiologic characteristics, manifests the pathologic changes which characterize the rheumatic process. It is also conceivable that susceptibility, specific or nonspecific, in the immunologic sense, may be a genetic character. This inherent susceptibility need not necessarily be considered specific for rheumatic fever.[42, 43]

The genetically susceptible individual manifests or develops the disease by the average age of 6 years. The interpretation of the age expression of rheumatic fever depends upon whether it is postulated that the expression of the disease is inevitable, or that nongenetic factors are necessary for the development of the disease. It is possible that both genetic and nongenetic factors are operative.

If nongenetic factors are solely responsible for the onset of rheumatic fever among susceptible children, the age expression of the disease may reflect the interval of time necessary for its development. This may be as short as one year, more often six years. It is then reasonable to speculate that the rheumatic process is the result of the response of susceptible tissues to specific or nonspecific agents which need not necessarily be bacterial in nature.

These studies indicate that the most important factor in the pathogenesis of rheumatic fever is the genetic susceptibility of the host. Further studies are necessary before it can be stated whether every susceptible individual in the general population develops rheumatic fever. Final interpretation of the age expression of rheumatic fever should reveal the factors responsible for the onset of the disease. At the present time it may be concluded that heredity is primarily responsible for the familial incidence of the disease, the age risk determining the time of occurrence of cases in the family.

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Erratum

In the Faber and Towne article, "Early Operation in Premature Cranial Synostosis for the Prevention of Blindness and Other Sequelae," on page 301 of the March issue of the JOURNAL, the legends B and C are reversed for Fig. 13. B should read "Oct. 11, 1939, etc." and C should read "Jan. 3, 1942, etc."

American Academy of Pediatrics

Proceedings

TWELFTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CHICAGO, ILL., NOV. 5-7, 1942

Round Table Discussion on Tropical Diseases

Chairman: Boyd Reading, M.D., Galveston, Texas.

Associates: Ludwik Anigstein, M.D., Ph.D., Assistant Professor of Preventive Medicine and Public Health, University of Texas School of Medicine; Formerly Assistant Professor in Parasitology, University of Warsaw, Poland.

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Yellow Fever and Dengue

Ludwik Anigstein, Galveston

Yellow Fever

Yellow fever is one of the tropical diseases which in wartime has often decided victory or defeat, disregarding the grand strategy of generals even before they had time to establish their headquarters. The disease has been known since Columbus landed in San Domingo where the men on his second expedition to America suffered heavily from yellow fever. Later the Caribbean Islands were time and again attacked by this disease which has played an important role in their political history. An outbreak of yellow fever in Puerto Rico at the end of the sixteenth century is responsible for the fact that this island is now American and not British. The independence of Haiti as a Negro Republic is due to an epidemic of yellow fever which wrought such havoc among the invading Napoleonic armies that they were compelled to leave the island. Out of an army of 30,000, 23,000 are said to have perished. This incident will remain forever a drastic example of devastation caused by yellow fever in days when no preventive measures against the disease were known. On the other hand, the construction of the Panama Canal would never have been accomplished if it had not been for the conquest of yellow fever by General Gorgas.

The cornerstone in the history of research on yellow fever was laid by the brilliant work of Reed, Carrol, Lazear, and Agramonte in Cuba (1901) who were the first to show that the causal agent could pass through filters. They also proved that the transmission of the disease under natural conditions takes place through the bite of the female mosquito *Aëdes aegypti* as predicted by Carlos Finlay. On the basis of the aforementioned discoveries, all further developments in our modern knowledge of yellow fever have been built.

In 1928 Stokes, Bauer, and Hudson made the important discovery that the rhesus monkey is susceptible to the disease and that the virus of yellow fever can be maintained in this species through many passages. In 1930 Theiler found that yellow fever could be transmitted to mice by intracerebral inoculation and that serial passages through the brains of mice produced a loss of virulence for monkeys. Instead of causing yellow fever, this fixed virus produced meningoencephalitis in susceptible animals. In contrast to this variation of the virus which exhibits definite neurotropic affinities, the pantropic or viscerotropic virus is capable of attacking not only ectodermal organs like the brain, but also the mesodermal kidney, spleen, and myocardium and the endodermal liver. We shall see later that the establishment of the neurotropic variety of the virus as well as its successful cultivation in vitro led to an important practical consequence: the development of a prophylactic vaccine.

These are the milestones we pass along the twisted road of yellow fever research. Before analyzing the recent developments, we must consider some fundamental facts on which their application is based.

First of all, the incubation period of this acute infectious virus disease is from three to six days. The practical consequence of this fact is that the quarantine of persons coming from an infected area need not extend beyond six days.

The next point is the presence of the virus in the circulating blood of a yellow fever patient only during the first three days of the disease. This fact is of epidemiologic importance because only during this initial period of high fever when the face is flushed and swollen, the eyes are injected, and the pulse is rapid can the virus be obtained from the peripheral blood by the female mosquito *Aëdes aegypti*, the principal vector.

After this period, beginning with the fourth day, a generalized jaundice of hepatogenic origin develops and simultaneously the fever subsides and the pulse rate gradually falls to the very low level of from 60 to 40 beats per minute. This symptom known as Faget's sign may be of diagnostic value. During this "period of calm" the blood of the patient is not infective to mosquitoes and he is, epidemiologically speaking, no longer dangerous. There is no characteristic skin eruption, but petechial, erythematous, or papular eruptions may appear and albumin may be found in the urine, sometimes in great quantities, together with suppression of urine. Casts are also abundant. Nausea and vomiting are common. The well-known "black" vomit is a most striking feature. It is vomitus of a coffee-ground color, consisting of digested blood mixed with mucoid fluid. Sometimes pure blood is thrown up from the stomach, while hemorrhages may occur from any part of the body. "Everything is congested at the outset, everything bleeds at the end" is a formulation of the disease. The majority of deaths occur on the fifth and sixth days. Relapses are rare and dangerous. The immunity is permanent.

Diagnosis.—Typical yellow fever may be confused with Weil's disease, infective hepatitis, bilious remittent fever, and blackwater fever. It is particularly Weil's disease which clinically may be mistaken for yellow fever. Within the first three days yellow fever may be transmitted experimentally by inoculation of the blood to rhesus monkeys which die after four or five days. When the blood is inoculated into the brain of a mouse, an encephalitis will occur. A retrospective diagnosis of yellow fever may be established by the presence of specific antibodies which will protect

mice against the virus. The post-mortem diagnosis is based on the histologic examination of the liver which shows fatty degeneration and midzonal necrosis. Pronounced changes are also found in the kidneys.

Since the virus is almost neutralized by the patient's antibodies by the fourth or fifth day of illness, we may presume that death is caused by a toxemia and particularly by the action of the toxins on the liver, heart, and kidneys.

Epidemiology.—Presumably yellow fever originated in Africa and then spread to this hemisphere in the days of slave trade. The development of epidemics requires a mean temperature of 75° F. and is aided by dampness. Due to the domestic habits of the mosquito vector, the disease is more prevalent in the urban centers along the tropical coasts of West Africa and South America. However, it has been found far inland following the lines of communications. [Maps were shown to illustrate geographic distribution of the disease.]

Similar to the well-established incubation period in the individual, which rarely exceeds four or five days, an epidemic also has its well-defined incubation period. It has been found that a period of at least a fortnight elapses between the arrival of a yellow fever patient in an uninfected area and the beginning of the epidemic. This delay, the so-called "extrinsic" incubation period, is to be explained by the incubation period in the mosquito which lasts about twelve days. After taking the infective meal the mosquito is harmless until about the twelfth day, from which time she remains infective for the duration of her life.

Epidemiologically, the cycle of infection, man-aegypti-man, is apparently very simple, and on this principle sanitary measures against yellow fever are based. The result is the eradication of the disease from Havana and Panama as well as from other cities on the Gulf of Mexico and the Caribbean Sea.

All was quiet on the western front until 1926 when yellow fever was unexpectedly declared in the interior of northeast Brazil in districts where there were no *Aëdes aegypti* mosquitoes. Further studies showed that there were some unknown epidemiologic factors responsible for yellow fever occurring in the absence of *Aëdes aegypti*. It was Soper who in 1932 discovered in Brazil an entirely new and unsuspected phase of the epidemiology of yellow fever, a jungle yellow fever. The term is of purely epidemiologic significance, since the classical yellow fever transmitted by *Aëdes aegypti* is identical with the jungle disease. The search for the responsible vector of jungle yellow fever resulted in the finding of a naturally infected, forest mosquito, *Haemagogus capricorni*, an inhabitant of treetops often not found at ground level. These peculiar habits of *Haemagogus* are responsible for the predominance of jungle yellow fever among men engaged in felling trees.

The above facts uncover the mystery of the epidemiology of yellow fever in areas where *Aëdes aegypti* is absent, but they also indicate that jungle yellow fever is a continuous source of virus for the reinfection of cities where *Aëdes aegypti* mosquitoes are present.

The last reports of the Rockefeller Foundation, from which most of the above facts are quoted, also uncover the mystery of the jungle fever in Central Africa, where *Aëdes simpsoni* has been incriminated as a new vector.

We may conclude, therefore that yellow fever is primarily a disease of jungle animals and that the classical form carried by the *Aëdes aegypti* to man is of a secondary cycle.

Protection Test.—It was found that the specific antibodies present in the serum of persons recovered from yellow fever remain in these individuals for a lifetime. If serum from such an individual is mixed with the yellow fever virus and then injected into a mouse, either intracerebrally or intraperitoneally, the animal will survive. This is the mouse protection test. The test is not only of diagnostic value but also of great epidemiologic significance because it serves to determine whether or

not yellow fever has been present in a region and to what extent. With this information, the occurrence of the disease can be identified and a map of its distribution plotted.

Immunity and Prophylaxis.—It was shown by Theiler (1930) that any strain of yellow fever virus may be rendered neurotropic by repeated passage through the brains of mice. Instead of producing a visceral yellow fever, such strains produce a fatal encephalitis in mice and monkeys when injected intracerebrally. In view of this neurotropism human immunization with this strain was originally always accompanied by protective immune serum.

In 1936 tissue culture technique was introduced to maintain the yellow fever virus in the laboratory. The culture medium consisted of Tyrode's solution, normal human serum, and minced mouse or chick embryo. The virus propagated successfully, and after numerous passages its virulence was found substantially attenuated, giving rise to a modification known as 17 D strain. This strain which lost its ability to produce yellow fever but retained its immunizing power was finally adopted for human immunization.

Until recently the vaccine was manufactured by the Rockefeller Institute of Medical Research, the number of doses for 1941 amounting to more than four million. In addition, the U. S. Army and Navy has ordered several million doses more during 1942. The production of the vaccine at present has been taken over by the U. S. Public Health Service with some modification of the technique of preparation.

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Dengue Fever

There are several characteristics which justify the parallel discussion of dengue fever and yellow fever, although each is a separate clinical entity and is caused by a different and specific virus.

The epidemiologic resemblance between yellow fever and dengue is very striking, indeed:

1. Dengue is transmitted by the bite of the infected female mosquito *Aëdes aegypti.*
2. The patient's blood is infective during the first three days of fever only.
3. Eleven days must elapse before a mosquito, which has fed on dengue blood, becomes infective.

This close similarity, the same vector, the same incubation period, the same period of infectivity, made it seem reasonable to believe that dengue fever might protect against yellow fever. It was found, however, that there is no immunologic reciprocity between the two diseases.

Geographic Distribution and Epidemiology.—The disease is widely distributed particularly in the tropics and subtropics where the conditions are favorable for the

existence of the mosquito vector *Aëdes aegypti* and for the continuity of the virus in nature. Dengue fever occurs in epidemic or pandemic outbreaks at irregular intervals. In the tropics the epidemic may last for several months or years. Sporadic cases may occur in the interepidemic periods, and from these cases further epidemics may originate. On the other hand, a dengue epidemic in the temperate zone is of short duration, limited to the warm season of the year only. A certain degree of immunity is conferred by the infection, the immunity lasting only a few months.

Symptomatology.—A detailed analysis and description of clinical manifestations of dengue fever was given by Rice in connection with the epidemic in Galveston, Texas (1922), which affected 30,000 people and was probably the largest epidemic of dengue fever in the United States. When a dengue epidemic is already in full swing, the recognition of the disease is comparatively simple, but the diagnosis may be more difficult at the early stage of the epidemic. This refers particularly to mild non-typical cases. The symptoms, including fever, may vary from epidemic to epidemic and from case to case.

The incubation period has been placed at from five to nine days. The onset is sudden, the initial fever high. About the third day the temperature drops to normal and remains so for from twelve to seventy-two hours. After this intermission, in typical cases the temperature rises again, resulting in the characteristic saddle-back type of fever chart. This second febrile attack is generally shorter and sometimes absent. It has to be emphasized that this saddle-back type of temperature is not a constant feature. Instead of a remission, continued fever may occur, lasting up to a week, but it also may be of one to three days' duration. The average fever duration is from about four to five days.

The pulse rate is slow and may be as low as 40 beats per minute. The initial fever is usually accompanied by a congestion of the face and a rash. The rash may be multiform and has a tendency to be bilateral and symmetrical. It is mostly seen on the face, forehead, neck, chest, forearms, palms, and soles and is variable in type: erythematous, roseolar, papular and hemorrhagic, maculopapular, or scarlatiniform.

Injection of the eyes, headache, and pain across the loins as well as pain in the joints, particularly the knees, are characteristic symptoms. Hemorrhage from the mucous membranes and bleeding from the nose, mouth, and ears are common. Gastric hemorrhages were observed and also the black vomitus. There is no jaundice. The complications of dengue fever are rare. Pericarditis, arthritis, and orchitis have been observed.

Although the mortality is negligible, the convalescence is very slow, lasting over a period of from one to three weeks after defervescence. Pain in the limbs and a state of mental depression are the most troublesome consequences.

Of the changes in the blood, the most constant feature is an extreme leucopenia, as low as 2,000 cells, produced by a decrease in lymphocytes and polymorphonuclear cells. Simultaneously there is an early increase in immature granulocytes resulting in a "shift to the left."

Pathology.—Owing to the low mortality there have been only a few reports of post-mortem examinations on dengue patients. In those single instances the special features were localized pulmonary and intracranial inflammation. A cloudy swelling of the viscera, particularly of the liver, which was also fatty, was noticed, as well as a few petechial hemorrhages in the gastrointestinal tract.

Diagnosis.—Dengue fever has been confused with a number of acute febrile conditions including yellow fever, malaria, the eruptive diseases of childhood, and influenza. Other denguelike fevers have been reported from various parts of the world; for example, the seven-day fever in India and the six-day fever in Panama.

At present the clinical diagnosis of dengue must be based on the typical symptoms, including the leucopenia, and these must be considered in connection with the epidemiologic features of the disease.

Treatment.—There is no specific treatment for dengue. The patient should be kept in bed in a screened room, and the treatment should be symptomatic. Salicylates and sedatives may be used to relieve pain. Regardless of the treatment used, the disease will run its course.

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Amebiasis and Other Protozoan Dysenteries

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Prevalence and Distribution.—The prevalence and distribution of amebiasis are world wide but somewhat commoner and much more serious in the tropics. In the United States, of 57,000 persons, in twenty-six surveys, 10.2 per cent were infected; of United States Naval recruits in 1939, 14.7 per cent from the South and 7.8 per cent from the North were infected; in some rural areas in Tennessee, 22 per cent were infected, and in some family groups, over 80 per cent; in China and the Philippines, over 20 per cent of the natives were infected. The incidence is highest in young adults.

Pathogenicity.—The pathogenicity is much higher in the tropics. Ten per cent of the infections produce dysentery; in temperate climates, far fewer. Carriers are common. Of 202 cases of accidental death examined in New Orleans within four hours, 13 (6.5 per cent) were infected. Five had lesions (superficial tissue invasion). Of eighteen experimentally infected in the Philippines, four developed dysentery. Of 15,000 infections in men in the Navy, 4.6 per cent developed dysentery. Craig believes that 65 per cent of the carriers have symptoms. Sapero reports of 216 nondysenteric infections in men in the Navy, 100 had symptoms.

The factors determining pathogenicity are still not fully known, but include pH of intestine, bacterial flora, previous lesions, bacteria accompanying amebae, mucosal irritation, diet (especially vitamins), virulence of strains, and acquired resistance. Westphall infected himself with washed amebae. No symptoms appeared for eight months. He and a colleague drank a suspension of amebic stool free of amebae. Mild dysenteric symptoms appeared in both for a few days. After twenty-eight days Westphall developed typical amebic dysentery.

Common nondysenteric symptoms are constipation with occasional diarrhea, anorexia, loss of weight, nausea, tenderness and pain in the abdomen, flatulence, tenderness over the liver, mild anemia, neurasthenia, headaches, fatigability, and nervousness. The symptoms often simulate appendicitis or peptic ulcer. A high per cent of obscure gastrointestinal ailments are amebiasis. Possibly all infections are harmful, but in many the damage is repaired as rapidly as produced.

Liver infections occur in 20 per cent of the dysenteric cases, sometimes when there is no history of dysentery. This is especially common where many white men in the tropics have little knowledge or are careless about care of their health. The symptoms are pain in the liver region, fever, leucocytosis, sorrowful expression of weariness and apathy, sallow skin, sunken cheeks, and dark-circled eyes. This infection is far commoner in whites than in natives (19:1) and more common in men than in women (10:1); it is rare in children under 10 years of age.

Diagnosis.—Diagnosis requires a competent technician. Trophozoites in a liquid or diarrheic stool and cysts in formed stools should be found. Faust's $ZnSO_4$ concentration method for cysts can be used. A complement fixation reaction is not practical for routine use. Cultures are helpful.

Mode of infection.—Only cysts survive outside the body. Cysts enter with contaminated water or food and pass the stomach best with liquids or when it is empty. These cysts are more easily destroyed than thicker-walled cysts of *Endamoeba coli;* therefore the latter type is twice as common. Amebiasis is more frequent when the stomach acidity is low.

Cysts survive several weeks if not desiccated but die within a few minutes on hands, except under long finger nails. They pass unharmed in droppings of flies and roaches (five to forty-eight hours); they reach vegetables, etc. by use of night soil in the Far East, soil pollution elsewhere. Water supplies are infected by monkeys; rats seem unimportant.

Cysts are not destroyed by chlorination but are caught by sand filtration; plumbing hazards are important; e.g., in Chicago World's Fair.

Treatment.—Treatment is now fairly reliable. Emetin is used for suppression of dysentery and various arsenic and iodine compounds for cure.

Diodoquin (adults 7 tablets per day for twenty days) is recommended by Craig as prophylactic.

Prevention.—(1) Boil water if it is not filtered; chlorination is inadequate. (2) Carbonation of water—believed to be safe after three days. (3) Do not eat raw vegetables unless immersed in boiling water or one hour in potassium permanganate (port wine color). (4) Protect food as much as possible from flies and roaches. (5) Practice sanitary disposal of feces; do not leave dysenteric stools uncovered and disinfect them. (6) Cyst carriers not desirable as food handlers, but the danger is not great. (7) Avoid excessive exposure, alcoholic excess, too peppery food, too much food, and other debilitating conditions. (8) Alcoholic and dietary excesses especially predispose to liver involvement.

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Other Protozoan Intestinal Infections

Other intestinal amebae (five species) are harmless except *Dientamoeba fragilis,* which causes gastrointestinal symptoms and low vitality. A ciliate, *Balantidium coli,* also is a cause of dysentery, but not always. There is a wide geographic distribution. Cases are reported from the Southern States, American tropics, Southeastern Asia, and North Africa. *Dientamoeba fragilis* is primarily parasitic in pigs; most human beings infected are associated with pig-raising. Malaria may cause dysentery in severe pernicious infections. Kala-azar sometimes attacks the mucosa of the large intestine. Coccidiosis fortunately is rare in man. Giardia is sometimes the cause of persistent diarrhea.

Bacillary Dysentery

Prevalence and Distribution.—Unlike amebic dysentery, bacillary dysentery appears in extensive epidemics, often following movements of armies. It is more frequent and virulent in the tropics and is caused by many varieties of bacilli. Shiga type is the most virulent (mortality 20 to 50 per cent), especially prevalent in Japan. It is undoubtedly widely disseminated by Japanese carriers.

Bacillary dysentery is the most important disease encountered by armies—the scourge of every great war. In World War I, bacillary dysentery, not the Turks, beat the British in Gallipoli; in World War II bacillary dysentery and malaria, not the Japs, beat the Americans on Bataan.

Epidemiology.—This disease resembles typhoid in some ways, but dysentery bacilli pass the stomach more readily than do typhoid bacilli; therefore, contaminated food plays a relatively larger part. The disease spreads rapidly in families, military barracks, camps, and institutions. As in cholera, hands of those attending patients are likely to become infected.

Flies play a much more important part than in typhoid. The bacilli live in the gut of a fly for five days; the role of roaches and ants is also important.

Bacilli live in moist, contaminated soil for weeks or months. They may even live through the winter in deserted latrines.

Predisposing Causes.—Predisposing causes are lowered resistance from fatigue, exposure, faulty diet, lack of vitamins, alcoholism, bowel irritation, and lack of acclimatization in tropics (new arrivals most prone to infection). Carriers outnumber the cases several to one.

Treatment.—Treatment consists of rest in bed, a liquid diet, and care of the heart, which is injured by toxin. Sulfaguanidine is highly effective—bacteriologic cures in from four to ten days; this makes possible treatment of carriers as well. Serum is used only in severe cases and the effectiveness is questionable. Bacteriophage treatment is also of doubtful value.

Prophylaxis.—(1) Always wash hands before eating. (2) Take great care of hands when attending patients. (3) Boil or pasteurize milk. (4) Use boiled or chlorinated water for drinking, washing dishes, etc. (5) Protect food from flies, roaches, and ants. (6) Disinfect stools of patients, soiled bed clothes, etc. (7) Vaccines are of doubtful value; there is available evidence against them, though sensitized vaccines or antiserum may lower mortality; oral vaccines are in the experimental stage.

Food Poisoning

Food poisoning is usually due to Salmonella or Staphylococcus infections. Salmonella infections usually originate from the intestine of food animals or rats. The meat may be contaminated during slaughtering or later by hands of butchers, etc.; also by flies, rats, etc.

Bacilli cause symptoms only when very numerous; they must have the chance to multiply in food; this is especially common in salads, barbecue, warmed-up food, smoked fish, etc., when not kept on ice. The bacilli are not spread by ordinary contamination as is dysentery.

Food poisoning staphylococci are especially common in custards, cream puffs, eclairs, custard pies, etc. The origin is uncertain but probably is from boils, stys, etc.

Food poisoning is especially common at banquets, picnics, etc. because food is prepared ahead in too large amounts to be kept in refrigerator.

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Cholera

Prevalence and Distribution.—India (Ganges delta) is possibly the only persistently endemic area; five pandemics occurred in the nineteenth century, all originating in India. There have been no reported cases in the United States since 1911. There were 2,500,000 deaths in India from 1923 to 1934. Recent outbreaks

have been in Iraq, Manchuria, Japan, Malaya, Celebes; cholera was widespread in China in 1937 and 1938.

Importance and Course.—Cholera is one of the most rapid and fatal diseases. In some epidemics the mortality is 80 per cent; average, 50 per cent. The incubation period usually is from one to three days only; then there is acute purging (rice-water stools), cramps, and collapse from failure of circulation. The bacilli remain in the intestine; the toxins are absorbed. There is extreme dehydration of the body. The disease may be fatal in twenty-four hours.

Epidemiology.—Cholera is conveyed principally by carriers and convalescents; it most frequently enters the body with water. As in dysentery, hands are important.

Contamination of water supplies in unsanitary regions is of prime importance; also uncooked fruits and vegetables, salads, shellfish and fish, and milk (especially milk contaminated after boiling). Contamination of ice by hands or infected foods is important. Flies are of far less importance than in dysentery; Vibrios soon die. Up to 20 per cent of contacts and up to 6 or 7 per cent of the general population during an epidemic become carriers. Purging or dysentery may precipitate a case.

Treatment.—Treatment consists of the following: Rest in bed, undisturbed, unmoved; no food except rice water or barley water; morphine to rest intestine during first twenty-four hours only; no purgatives. Most important is to replace the fluid loss by hot intravenous saline, 2 L. in from twenty to thirty minutes repeated at six- to eight-hour intervals; also saline enemas. Recently sulfaguanidine has been reported to be very helpful. Bacteriophage also has been very beneficial—1 dram every 30 minutes. Bacteriophage is the basis of cure when it develops in an individual—it stops epidemics the way Vibrios cause it.

Prophylaxis.—(1) Protection of water and wet foods: drink or wash dishes in only recently boiled or chlorinated water protected from flies; eat no uncooked food, especially lettuce, celery, shellfish, salads; dip oranges and bananas in boiling water. Put no fish on ice or in icebox, and protect icebox from contamination. (2) Disinfect patients' excreta. (3) Disinfect wells with chlorine or treat with bacteriophage; one area in Assam where wells were treated with phage remained free five seasons, while neighboring areas had an average of one outbreak per season. (4) On march, add 2 gr. sodium bisulfate to 1¾ pints of water. (5) Wash hands before eating and after caring for patient. (6) Eucalyptus oil, 10 minutes daily, has been advised as prophylactic; also acid drinks, but these may defeat purpose by upsetting digestion. (7) Avoid purgatives and anything lowering resistance. (8) Value of vaccines is difficult to evaluate because of no adequate controls, but they seem to reduce materially case and mortality rates; vaccines are widely used in Asia. Oral vaccine, three to five doses (200 billion dried organisms), is apparently equivalent to one subsequent inoculation of four billion. (9) Serum treatment is unsatisfactory.

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Helminthic Infections

I. Hookworm Infection.—

Geographic Distribution and Prevalence: Hookworm infection is important in the Gulf Coast States of the United States, Northern South America and the Southeastern Brazilian Coast, Egypt, West and Central Africa, Southeastern Asia and Southern China, and some of the South Sea Islands.

Factors Determining Importance: Since the life cycle of the hookworm involves development of larvae in the soil, prevalence is determined by conditions favorable for such development, and human contact with infested soil.

Environmental factors are warmth; moderate well-distributed rainfall to keep soil constantly moist but not saturated; high humidity; excessive irrigation in lieu of rainfall (Egypt); drainage to prevent flooding, but not to allow too rapid draining off of water where rainfall is light; sandy or loamy soil; vegetation providing shade; coprophagy may be harmful or helpful to hookworms—in the case of cattle and ronches (in mines) it is harmful.

Regarding human factors, the white race is the most susceptible; injuriousness increases with age and is greatest in females, especially during pregnancy; agriculture and mining especially favor the hookworm; in the Far East, due to use of night soil, the hookworm is strictly agricultural, elsewhere merely rural; some crops favor the hookworm—especially coffee, tea, sugar, cacao, bananas, mulberries (in China); defecation habits are important; wearing footgear is protective; expectoration is helpful; an adequate diet has a neutralizing effect, especially good iron intake; the number of hookworms harbored is important.

Treatment: Tetrachlorethylene best; carbon tetrachloride dangerous if calcium deficiency exists. Iron administration often indicated prior to anthelmintic treatment.

Prevention: Abolition of soil pollution; treatment, est. mass treatment; disinfection of soil or feces (seldom practicable); wearing of footgear.

Creeping Eruption: Frequently develops from invasion of skin by larvae of hookworms of cats and dogs.

II. Strongyloides.—Strongyloides is the common cause of diarrhea in the tropics. Larvae develop in soil as do the hookworm larvae, but a free-living generation may be interpolated.

Strongyloides is distinguished from the hookworm by the absence of eggs in feces (only embryos present) and by minute structure of larvae, especially of infective larvae after culturing.

The mode of infection and prevention is same as for hookworm, but treatment is different—strongyloides requires gentian violet.

III. Ascaris and Trichuris.—Prevalence and Distribution: Ascaris and trichuris are common in all warm moist climates. Eggs undergo development outside the body but do not hatch. Climatic requirements are the same as for the hookworm.

Epidemiology: Children especially are frequently infected where there is dooryard pollution, and abundant warmth, moisture, and shade. The eggs are conveyed to the mouth by dirty hands. Natives are often infected from unsanitary water; raw vegetables grown in polluted soil are less important than hands and water.

Treatment: Treatment consists of oil of chenopodium or hexylresorcinol therapy.

Prevention: Wash children's hands frequently; keep after them about putting dirty fingers in mouth.

IV. Oxyuris (Pinworm).—

Occurence: More common in temperate climates than in tropics; incidence is highest in school children, up to 40 per cent or more; the occurrence is more frequent in whites than Negroes.

Life Cycle: The eggs develop to the infective stage in a few hours; do not hatch.

Mode of Infection: Eggs resist desiccation and get into the air from bed clothes, towels, and underwear and may be breathed in or conveyed to mouth by hands directly, or with dust, soap, etc.

Diagnosis: Fecal examination is inadequate; anal scraping is necessary, NIH swab especially good.

Treatment: Gentian violet, ½ to 1 gr. three times daily, seven to eight days; it is best to treat all members of the family at one time.

V. Cestode Infections.—

Taenia saginata: From uncooked beef.

Taenia solium: From uncooked pork; more dangerous because if reversed peristalsis carries segments to the stomach, embryos may be liberated from eggs and cysticerci develop, frequently in brain or eye.

Hymenolepis nana: From contamination of food by droppings of rats or mice. This develops directly without an intermediate host.

Diphyllobothrium latum. From uncooked fresh-water fish (pike, pickerel, turbot, etc.) in Canada, around the Baltic, and in Siberia particularly. It may precipitate pernicious anemia.

VI. Trematode Infections.—

Schistosomiasis: Important in the West Indies and Northern South America, Africa, and the Far East. Infection comes from bathing or wading in polluted water harboring the snails that serve as intermediate hosts. Larval forms (cercariae) penetrate the skin.

Fasciolopsis: Cercariae, after escaping from snail host, encyst on water vegetation, especially water chestnuts and caltrop or ling; very prevalent in China. Fasciola (liver fluke of sheep and cattle) sometimes infests man, especially in Cuba; the liver fluke has a similiar life cycle to that of Fasciolopsis; it is conveyed by watercress.

Cercariae encyst in flesh of fish or crabs. Beware of improperly cooked fish in the Near and Far East and of crabs and crayfish in the Far East.

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Summary of Precautions to Avoid Infections of the Alimentary Canal in the Tropics

General Hygiene.—Avoid alcoholic excess, overeating, too highly spiced food. Keep up general resistance when possible by plenty of sleep, regular hours, avoidance of excessive fatigue or exposure. Be more than normally careful of vitamin intake, especially B_1 and C. Much tropical neurasthenia is due to inadequate B_1; supplementary thiamine, ascorbic acid, and vitamin A are desirable when available. Avoid cathartics, especially irritating ones.

Water.—Except in a few places where properly filtered and chlorinated water is available, use only boiled or privately chlorinated water, or stick to carbonated drinks, beer, or milk from a freshly opened cocoanut. Chlorination does not kill amebic cysts. In the face of epidemics, especially of dysentery or cholera, use only boiled water for dishwashing too.

Milk.—Always boil or pasteurize milk after it reaches you if brought by native servants, even if previously pasteurized. In most places, it is better to stick to canned or dried milk.

Vegetables.—Eat no raw vegetables, or fruits like strawberries, grown in polluted soil, unless first soaked for one hour in $KMnO_4$ (port wine color) or dipped in boiling water. See that the servants actually cover them. Avoid water chestnuts or other raw water vegetation in China and watercress from water to which cattle, sheep, or goats have access.

Meat, Fish, etc.—Have beef and pork cooked until redness is gone. Eat only thoroughly cooked fresh-water fish—important in Canada, Baltic region, Siberia, and

Near and Far East. Where cholera is present, do not put raw fish in the icebox. Do not leave meat, fish, milk, or custard dishes out of refrigerator overnight.

Flies, Roaches, Ants, etc.—Protect food to the fullest extent possible, particularly when there is danger of dysentery or cholera. It is important to protect food from rats and mice also.

Hands.—Always wash before eating or after attending dysentery or cholera patients. Keep after children about keeping fingers out of mouth.

Servants.—In face of an epidemic of dysentery or cholera, it is probably safest to treat with sulfaguanidine unless laboratory examination to show them not infected is possible. Insist on frequent washing of hands.

Bathing, etc.—In areas where schistosomiasis exists, do not bathe or wade in water possibly polluted by excreta (including urine) of natives. Do not permit children to run barefoot or play on soil polluted by either human beings, or cats and dogs (latter not so serious, but may lead to creeping eruption).

Disposal of Excreta.—Disinfect excreta of bacillary dysentery and cholera patients and carriers. Prohibit soil pollution by servants. Make latrines fly-proof. Disinfect soiled bed clothes, etc. of patients.

Vaccines, Sera, etc.—Of doubtful value for dysentery but are indicated for cholera and typhoid. Oral cholera vaccine in several doses is equal to one subsequent inoculation. Bacteriophage treatment is also valuable for cholera patients and for infected wells.

Laboratory Diagnoses.—In case of dysentery or obscure gastrointestinal symptoms have a microscopic examination made for amebae or other protozoa, and bacteriologic examination with agglutination for dysentery bacilli or cholera vibrios. Periodic examination of children's stools for worm eggs is desirable. If oxyuriasis is suspected, examine anal scrapings.

Practical Aspects of Malaria in the Tropics

Louis Laval Williams, Jr., Atlanta

As pediatricians in a northern climate, you have doubtless seen little, if any, malaria in children, and to you it is a disease of minor importance. If you are going into service, the minute the plane or transport sets you down on a tropic or subtropic shore, you will meet malaria as your strongest adversary in the battle to keep the troops well and efficient. In World War I malaria led the list of casualties due to disease, although compared with this war, few men were in tropical countries. The infection rate, then, was high, as few precautions were taken. Today, in the United States, malaria control has come "of age," so we should send very few men abroad harboring the parasites. Furthermore, we have learned to safeguard our troops in the field with prophylactic quinine or atabrin, protective clothing, mosquito nets, protective spraying on night work, and hospitalization for severe cases.

If you had seen, as I have seen, in the hyperendemic areas of China and India and the endemic sections of Puerto Rico and Italy, the thousands of scrawny children with their abnormally protuberant abdomens due to enlarged spleens, two to ten times normal size, you would realize the potential crippling effect of malaria upon the troops.

In our country, we do not think of malaria as a disease of high mortality, but we must learn to think of it that way, for most of the troops we are sending into the tropics are nonimmune and therefore malaria among them will be virulent. Even in India where immunity must be built up to its maximum, the death rate is a million or more a year.

Care of malaria patients among our armed forces cannot be placed solely in the hands of physicians accustomed to treating the disease, as there are so few of them, so all medical officers going into the tropics should have a working knowledge of the diagnosis, treatment, and control of malaria.

Diagnosis.—Wherever a microscope is available, the diagnosis of most cases of active malaria is simple if a blood slide is taken from all patients with fever or collapse. The presence of the parasite indicates specific treatment. If thin films are taken, a fifteen-minute examination may be required and, if negative, should be repeated on successive days. A thick film is preferable. The slide should be cleaned in soapy water, rinsed; soaked in alcohol, and rubbed dry. The finger should be cleaned in alcohol and rubbed dry, then stuck and a large drop of blood squeezed. The slide should be inverted over the blood drop and rotated until a hanging drop is secured the size of the thumbnail. Print should be barely perceptible through the drop. If not, the blood should be spread with the corner of another slide; then lay the slide flat, protect it from flies, and allow it to dry thoroughly (three or more hours). The slide should be placed on end (or edge) in a small container of aqueous giemsa (one drop of alcohol giemsa to 1 c.c. of neutral distilled water) and left for three quarters of an hour. A three- to five-minute examination of such a thick film will reveal parasites which could only be found in an hour on thin films.

Often a microscope is not at hand, particularly with combat forces in the field. Diagnosis must be made from signs and symptoms. We like to think of classical malarias ushered in with a low fever followed by a shaking chill lasting thirty minutes to an hour, then a great rise in temperature lasting from one to two hours accompanied by malaise and headache and terminating with a profuse sweat, the temperature reaching normal five to eight hours after the chill. This picture may be seen in well-developed primary attacks or relapses from infrequent infections. Patients have built up only a little immunity. Where immunity has been built up through repeated attacks, it is not at all unusual that the chill, even a chilly feeling, drops entirely out of the picture. In primary attacks there may be nearly a week of low fever with no chill, for chills do not develop until the fever is over 100° F.

In such cases one is inclined to rely upon the textbook description of benign tertian with its fever today, normalcy tomorrow, and fever the next day; or of quartan with its sharp elevation of fever today, normalcy tomorrow and the next day, followed by a few hours of fever on the succeeding day; or of malignant tertian (estivo-autumnal) with its classical picture of continued fever with one remission to normal each day. Unfortunately these clear-cut pictures are not always found. Malignant tertian may commence with the benign tertian cycle, not becoming remittent until late in the attack, perhaps too late for successful treatment. Benign tertian and quartan, particularly quartan with a new cycle developing to replace an existing cycle, may show a fever chart of more or less continued fever with irregular remissions. What is the clinician to do? He attempts to exclude other infections, feels for the spleen, observes the anemia, and falls back on suspicion of malaria.

Fortunately, in victims with no immunity, the classical picture of chills and fever may be expected before a week has passed, and therefore lack of splenic enlargement does not upset the diagnosis. Where there is active immunity to reduce or prevent the chill, then either immediately or very soon the enlarged spleen may be felt. In benign tertian the prodromes are rather definite: periodic feelings (every other day) of lassitude, malaise, headache, and joint and muscle pains. In all species of infection an attack is preceded by apprehension, lassitude, and an "achy feeling." Such a history, often volunteered by the patient, is significant and should be regarded as a valuable signpost. In any event, a therapeutic test should be given to any patient with undiagnosed fever in the tropics. If it is malaria, most patients will definitely respond in one or two days to proper treatment.

Malignant tertian is the malaria to fear. If the immunity mechanism of the body develops fast enough, it will save the life of the patient. Unfortunately, in a considerable number of patients the parasite *(Plasmodium falciparum)* experiences a sudden acceleration of reproduction and overwhelms the victim. When this parasite is known to be present or is strongly suspected, treatment should be immediate and

vigorous. If a microscope is available, then this parasite should be watched closely and the number of parasitized cells per hundred blood cells should be counted regularly. If 5 per cent of the red cells are infected, it is sign that the immunity mechanism is breaking down and the most vigorous type of treatment should commence without delay.

Malignant tertian sometimes manifests itself abruptly in a cerebral form, and individuals have been known to fall as though hit. Collapse with unconsciousness should always arouse a suspicion of malaria even though the fever be low, normal, or subnormal. Collapse without unconsciousness with diarrhea and subnormal temperature are the principal indications of algid malaria, the intestinal form. This requires as prompt and vigorous treatment as does the cerebral form.

Blackwater fever (hemoglobinuric fever) occurs principally in newcomers to intensely malarious countries, rarely before three months of residence and mostly in their second year. It is never seen in individuals who have not had repeated infections with malignant tertian, and its incidence is roughly comparable to the amount of malignant tertian in the local population.

The disease starts with a rigor lasting from one-half to four hours, followed by a low-grade but persistent fever. The patient is severely prostrated. Both the spleen and liver are enlarged and are tender as long as the fever lasts. Hemoglobinuria usually appears at or soon after the rigor but does not tend to persist. There is some suppression, and jaundice seems to be in proportion to the suppression, being greatest with anuria. Blood destruction is the outstanding feature, and the patient may lose a million red cells in twenty-four hours and may lose as much as four million in a few days with hemoglobin falling as low as 10 per cent. Microcytes and malformed new red cells, indicative of hematopoietic activity, may be all that is seen through the microscope. The death rate is high (20 to 30 per cent) mostly in the first week. Fear the worst if there is uncontrolled vomiting or hiccoughing, or if the urine is suppressed.

Blackwater fever is easy to diagnose if the discolored urine is seen. Hemoglobinuria usually lasts less than twenty-four hours and may be a symptom for as short a period as three hours, though it may persist for a week. The patient, however, may be sick for thirty days. As a matter of practical application, if a hemoglobinuric specimen of urine is not collected or if no competent observer has observed the characteristic urine (from light red to black), then in all probability a diagnosis will not be made under field conditions. If the spleen and liver are enlarged and tender, blackwater fever should be suspected, especially if a low-grade fever persists with headache, malaise, and jaundice, and if the microscope shows no parasites. If this disease is seen in the field, malaria will probably be suspected and standard treatment given without particular benefit to the patient and, in the case of quinine, with deleterious results.

Treatment.—The time to treat a malarial attack is immediately upon diagnosis. A great deal has been written concerning the development of immunity in malaria and the advantages of permunition, which means permitting the attack to proceed for a number of days with only a fraction of normal therapeutic doses, thus allowing a fairly large number of parasites to remain in the circulating blood in order to increase the immunity and reduce the number and severity of subsequent attacks. This is all very well for a hospitalized patient with benign tertian. It is a dangerous procedure with malignant tertian anywhere. In the majority of cases some infection will remain in the individual anyway, slowly building an immunity, for treatment removes the parasite only from the peripheral circulation. When malaria is definitely known to be present, unless otherwise indicated, the safest procedure is to give a standard treatment immediately.

A malarial attack is usually accompanied by a badly upset stomach. This often prevents medication by mouth. An effort should be made to control the vomiting, for

antimalarials are best introduced via the stomach. The malaise present is intensified by the acidosis that accompanies an attack with most forms of the malarial parasite, though most particularly with malignant tertian. The best hospital treatment includes a preliminary purgation and alkalization of the patient which usually controls the vomiting and permits treatment by mouth.

In hospital patients the Sinton treatment is excellent. Following preliminary dosage with alkaline salts, one-half hour later, at least, quinine is given in liquid form or atabrin in tablets. The treatment mixtures and dosages are given in Table I.

TABLE I

	SINGLE DOSE (1 OZ.)	TOTAL FOR 7 DAYS
Alkaline Mixture		
Sodium bicarbonate	60 gr.	1,380 gr. (92 Gm.)
Sodium citrate	40 gr.	920 gr. (60 Gm.)
Calcium carbonate	3 gr.	69 gr. (4.6 Gm.)
Water to make	1 oz.	23 oz. (690 c.c.)
Quinine Solution		
Quinine sulfate	10 gr.	210 gr. (14 Gm.)
Citric acid	30 gr.	630 gr. (42 Gm.)
Magnesium sulfate	60 gr.	1,260 gr. (84 Gm.)
Water to make	1 oz.	21 oz. (630 c.c.)

After purgation, three doses of the alkaline mixture are given at intervals of one-half hour. One-half hour after the last alkaline dose, a dose of the quinine mixture is given. Thereafter during the first day two more doses of the alkaline mixture are given, each followed (after an interval of one-half hour) by a dose of the quinine mixture. Each of the above formulas constitutes a single dose. For the next six days, three time a day, before meals, a dose of the alkaline mixture should be given, followed after an interval of one-half hour by a dose of the quinine mixture. If quinine is not available or if the clinician prefers, atabrin may be substituted. The dose of atabrin is 0.1 Gm. (1½ gr.) three times a day, for from five to seven days.

Along with quinine or commencing a few days after the last dose of atabrin, plasmochin may be given. The dose of plasmochin is 0.02 Gm. (⅓ gr.) once each day for seven days. This has no effect on the clinical attack, but experience has shown that subsequent relapses are less frequent. Always complete the treatment. Never stop on cessation of symptoms. Incompletely treated attacks always relapse.

Malignant tertian demands the most careful treatment. This form of malaria tends to attack some particular organ or system and is usually a severe infection. It may attack the nervous system causing hemiplegia, paraplegia, epileptic attacks, neuritis, persistent delirium, and coma. Aphasia may occur and various psychoses. The disease has simulated dysentery, appendicitis, and peritonitis; it has appeared as an angina and has produced symptoms of thrombosis, hemorrhage, and heart failure and caused rupture of the spleen. It can produce a definite pneumonia and bronchitis. It may cause nephritis or nephrosis with albumin and hematuria. The cerebral form is a general encephalitis, often with clogging of the capillaries of the brain. When dangerous symptoms appear showing infection of such, it is a definite indication that vigorous treatment has been delayed unduly.

Clinical symptoms appear in a primary attack when the parasites infect approximately $\frac{1}{1000}$ of 1 per cent of the red blood cells. It is readily apparent then that infection of 5 per cent of the red cells is an excessive invasion. An infection of this severity or the appearance of symptoms, indication of any of the special organ or system invasions, is an indication of the necessity for the most vigorous treatment—maximum dosage, intramuscular, and sometimes intravenous, medication.

The first procedure in vigorous treatment is to give quinine by mouth and into the muscles, a total of 45 gr. the first day. If the vomiting is excessive, an attempt should be made to control it so that the oral route may be used. Alkalies by mouth may be successful; if not, alkaline lavage should be tried. Intravenous alkali to reduce acidosis is justified. If these measures fail to permit quinine or atabrin to remain in the stomach, then the clinician is justified in using cocaine, followed by a liquid solution of quinine. At the same time quinine should be given intramuscularly.

In the field or with mobile forces, the preliminary purgation and alkalinization may be impossible. The important thing is to get quinine or atabrin into the system as quickly as possible. Start right away with 10 to 15 gr. capsule doses of quinine sulfate, or bisulfate tablets, after meals, three times a day. If atabrin is preferred, give a 0.1 Gm. tablet (1⅔ gr.) three times a day, after meals. In most patients, after the paroxysm, vomiting ceases, and oral treatment is easy. If vomiting does not stop naturally after a paroxysm, it must be controlled, even to the use of cocaine, unless intramuscular preparations of quinine or atabrin are available. Usually they are not in the field.

If experience has shown that the locally prevalent strain of malignant tertian is very virulent, then look with suspicion (in the field) on all cases of fever or collapse and commence treatment for malaria immediately. The occasional damage if it is some other condition, such as blackwater fever, will be far outweighed by the greater saving of life.

If the patient is showing signs of impending collapse in hospitalized cases, then the intravenous route is definitely indicated and may be the only measure likely to save life. A convenient preparation is quinine hydrochloride (or dihydrochloride) 5 to 7½ gr. dissolved in from 150 to 250 c.c. sterile normal saline with ½ to 1 c.c. of 1:1,000 adrenaline. Take at least a quarter of an hour in injecting this dose and preferably one-half an hour. Repeat this dose every eight hours until the patient can take medication by mouth. Atabrin is as effective as quinine if 3 gr. are given in 200 c.c. of saline at twelve-hour intervals. These are large quantities of fluid into the vein of a collapsed patient; therefore, the blood pressure must be taken continuously. Progressive reduction of pressure requires cessation of injection. As soon as drugs can be taken by mouth, cease intravenous injection.

There is no specific treatment for blackwater fever. All therapeutic measures are aimed at conserving the strength of the patient and alleviating symptoms. Keep the patient warm and quiet and force alkaline fluids to the limit (10 gr. of sodium bicarbonate every one to two hours). During the vomiting period give fluids intravenously, at least 2,000 c.c. per day, adding some sodium bicarbonate and glucose up to 5 per cent. If vomiting is not soon controlled, give ¼ gr. of cocaine in a little water by mouth. Continue alkaline salts until the urine is alkaline to litmus, and then modify dose to keep it so.

If anemia becomes severe, give repeated blood transfusions. If plasmodia are found, withhold specific treatment until convalescence is established, avoid quinine, and give atabrin 0.1 Gm. (1⅔ gr.) three times daily for five days.

Blackwater fever tends to recur, especially if the patients remain in a hot climate. They should be removed to cool zones as quickly as possible and kept there for prolonged periods.

Malaria Control.—The best method of malaria control is control of production of the malaria-carrying anopheline. This method is not only possible but advisable at more or less permanent locations such as a work camp, general headquarters, or a base hospital or a training area. The medical officer should always attempt to pick the camp site. In general, elevated areas should be selected which have the least amount of water within one-half a mile and are over one-half a mile from native

villages which may be prolific sources of infection. Accessibility to water should not be the deciding factor in locating labor camps in malarial areas. Thousands of coolies who grubbed out the Burma Road with their hands died because their camps were in the irrigated valleys instead of in the high hills.

The local anopheline vector should be ascertained if possible. It cannot be expected that the average medical officer will be an expert in any form of malaria control and less likely that he will be familiar with the particular anopheline of his area. He may not be familiar with the pond, river, swamp, fresh and salt water breeding habits of the South and Central American coastal vector, *Anopheles albimanus*, nor with its two-mile infective flight range. He may be unfamiliar with the house-frequenting habits of the African *Anopheles gambiae* and its breeding places, sometimes in streams and ponds, sometimes in ditches and temporary rain pools, or occasionally in artificial containers. He may have to contend with the Indian *Anopheles culicifacies* with a flight range of approximately a mile and breeding places in streams, ponds, river overflows, irrigation drainage, or irrigation wells which often dot agricultural countryside; or he may have to contend with *Anopheles stevensi* which sometimes invades deep, dark drinking water wells. He is more than likely to meet the Asian *Anopheles minimus* with its short half-mile infectious flight and which breeds in the waters of the sunlit stream edges, irrigation ditch edges, hillside rivulets, and often in the thin film of foot-of-a-hill seepage outcrops.

At least the medical officer can make inquiry of the local health administration concerning the type of vector and its usual habits. Guided by such advice he can effect the organization of a mosquito control force and remove by drainage many of the near-by water collections and apply oil or a light dusting of Paris green to the remaining characteristic waters at weekly intervals. He may not prevent all malaria transmission, but through these measures he can minimize it.

Although a number of anopheline species may be present at each locality, it is unusual that more than one species of Anopheles is an efficient vector of malaria at any particular place. Where two species do transmit the disease, they are usually of the same group with similar breeding habits. Malaria control, through preventing the production of anophelines, is therefore rarely wholesale anopheline control but can be confined to species control, thereby removing from attention considerable bodies of water. For instance, *A. minimus* and some *Anopheles maculatus* are found breeding together in the sunlit stream edges of irrigation ditches and drainage ditches of the rice field areas of Southwest China. Great numbers of *Anopheles hyrcanus* are simultaneously found in the more extensive waters of the flooded rice fields themselves. *A. hyrcanus* does not transmit malaria, thus eliminating most of the water from consideration, and attention may be confined only to the sunlit portions of continously moving water.

At both fixed and semimobile locations and without knowing the specific vector of malaria one can minimize disease transmission by insecticide spraying within the houses, barracks, and tents. The anopheline is not naturally infected and, after securing an infectious meal, must incubate the parasite approximately two weeks before she can transmit malaria. The most dangerous ones are the mosquitoes which habitually return to human habitations for blood meals. After feeding, most of these anophelines roost nearby during the early stages of digestion. Therefore, if all places of human congregation are regularly sprayed with a good insecticide, then a large number of anophelines during the extrinsic incubation period will be killed before they become infectious.

The best antimosquito insecticide is pyrethrum. The pyrethrines of the pyrethrum flower are easily extracted and are concentrated in various forms. These extracts can be mixed with volatile oil or with the well-known refrigerant freon. A very small quantity released as a fine mist in a room will infiltrate into the dark corners and into the cracks of a wall and will kill all mosquitoes with which it comes in

contact. The best interval of spraying is twenty-four hours. Spraying as infrequently as once a week has, in some places, greatly reduced malaria rates. In other places twice a week has been necessary to obtain equal results. Daily spraying is safest.

As small a quantity as 1 c.c. of a 2 per cent pyrethrine extract in the form of a fine mist will kill all of the mosquitoes in 1,000 cubic feet of air space.

Some anophelines enter quarters at night to feed and leave the quarters before sunrise. Therefore, bed nets should be used wherever screened quarters are not available. The average cot or single bed sleeper will roll around enough during his sleep to assure that the face, shoulder, or arm will be pressed against the bed net and thus render its protection ineffective. To protect against this nighttime movement, the bed net should have a foot or foot-and-a-half band of heavy cloth sewed to it with its bottom at the mattress level, a band to roll against. This is important.

Some protection may be given individuals who must remain outdoors after dusk, which is the anopheline feeding period. Repellents on the skin and the clothing give some protection, and it is advisable to use them when they are available. Citronella is moderately effective and cedar oil is more so. There are various proprietary preparations which are useful, but each should be tested before reliance is placed upon it. The clothing is important for those who must remain outdoors after dark. Where mosquito density is heavy, head nets and gloves should be used. If available, mosquito boots should be worn. These are commonly used in many parts of the tropics, particularly India.

If any of these methods are impractical or are obviously insufficient, especially with highly mobile troops, prophylactic medication should be given regularly. It should be remembered that drug prophylaxis does not prevent infection but in 95 to 99 per cent of the cases it does prevent development of a clinical attack. If quinine is used, 5 gr. should be given each day to each individual, preferably after a meal. If atabrin is used, it should not be given daily. The atabrin should be taken every third or fourth day, giving .012 Gm. (3 gr.) during the day, divided into two doses (0.1 Gm.), preferably after meals. When individuals are removed from danger of malaria infection and the prophylactic medication is discontinued, one should be on the lookout for clinical malaria. The human system does not always take care of the minimum infection which may have been acquired during the prophylaxis, and the parasite often increases with considerable rapidity upon withdrawal of the drug.

The military surgeon should be particularly aware of malaria. Exposure often activates a latent malaria. Hemorrhage through wound or operation will almost always activate a latent infection, and postoperative temperature elevation in the tropics is not always a sign of sepsis—it is often a malaria infection which requires immediate treatment.

Malaria is found at its worst between 30° north latitude and 30° south latitude, becoming more intense as the equator is approached. It is usually more prevalent where water is abundant and elevations are below 3,500 feet and the warm rainy season is long. Of over 180 species of anophelines, about thirty-five are natural vectors of malaria. They have prevented any real development of the tropics. The populations which live among them too often merely learned to live with malaria, not to work with it. If large numbers of nonimmune people are sent into the tropics, they will not work with it either, unless they are protected.

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Army Medical Bulletin No. 59, January, 1942.

DISCUSSION

DR. P. C. WALDO, OAK PARK, ILL.—Does rotenone kill mosquitoes as well as pyrethrine?

DR. WILLIAMS.—Not so well, but it does work. Definite quantity of pyrethrine necessary is not known, but experiments have shown that mosquitoes are killed in fifteen minutes by a minute amount on one leg. Freon Bomb is 0.8 ounce of 20 per cent pyrethrine extract and 15 ounces of freon. On contact with the spray, the mosquito drops immediately.

Medical officers should read Army Medical Bulletin 59, January, 1942, put out by the Surgeon General's office for more data on this.

DR. PHILLIP ROSENBLUM, CHICAGO.—Is it possible to have malaria and repeated chills and not find the organisms? [Cites case in which malaria was suspected, but no organisms were found.]

DR. WILLIAMS.—It has been found that one parasite to 100,000 red blood cells may cause symptoms; that is why thick smears have been advocated. It is hard to believe that this was a case of malaria if the spleen smear was negative and the preagonal smears were negative, because these latter smears are usually loaded with all forms. Children may have atypical attacks.

Not far from Chicago, in Michigan, a family infected with malaria moved into the community recently and infected several individuals; then too, a girl's camp near Chicago recently had an epidemic of malaria from visitors from the South. Impounded water along the rivers in this vicinity may be a source of the mosquitoes, and years ago there was considerable malaria in Indiana and Illinois. Latent malaria may show up on moving to a higher altitude.

DR. CAMPBELL HARVEY, PONTIAC, MICH.—We not infrequently see cases of malaria in the industrial communities around Pontiac.

DR. J. V. GREENEBAUM, CINCINNATI.—Can afebrile malaria occur in children?

DR. WILLIAMS.—Yes, although it is not common.

DR. ROBERT BLESSING, FORT LAUDERDALE, FLA.—Does the spleen remain enlarged indefinitely?

DR. WILLIAMS.—In some cases, the spleen may cease to be palpable within a few weeks; in other cases after several months. Splenomegaly per se is not a reliable diagnostic index.

DR. GREENEBAUM.—Do you consider atabrin as satisfactory as quinine?

DR. WILLIAMS.—The literature shows it to be about as good; some respond to atabrin when they will not to quinine and vice versa. Alternate treatment between the two in relapsing cases may be better.

CHAIRMAN READING.—What are the toxic symptoms of atabrin medication?

DR. WILLIAMS.—Vomiting, cramps, transient yellow color to the skin, and psychotic symptoms.

DR. M. L. BLATT, CHICAGO.—What is the dosage of atabrin as a prophylactic?

DR. WILLIAMS.—Give 3 gr., divided into two daily doses, about twice a week. This is not 100 per cent effective but will limit the incidence to 25 to 40 per cent.

DR. PERLSTEIN.—Are the sulfonamides of any value in malaria?

DR. WILLIAMS.—The results have been inconstant and unpredictable as compared to quinine and atabrin.

DR. PERLSTEIN.—Where quinine is not tolerated orally, is it possible to give it rectally?

DR. WILLIAMS.—It is very irritating by this route. Give it intramuscularly, if orally intolerable.

DR. WALDO.—For how long after the first attack is it possible to have a relapse?

DR. WILLIAMS.—Possibly as long as a year.

DR. WALDO.—Is it possible to go as long as three years?

DR. WILLIAMS.—You would suspect quartan in that event. Some may even last from fifteen to sixteen years, but these are museum cases. Estivo-autumnal type is usually gone after a year. Malaria due to transmission by blood injected is not severe and responds quickly to therapy.

DR. E. S. GOODWIN, ALBANY, N. Y.—Say more about blackwater fever.

DR. WILLIAMS.—I was afraid some one would ask about this. It is never seen except after repeated infections.

CHAIRMAN READING.—How far will a mosquito that is a malarial vector fly?

DR. WILLIAMS.—Two and one-half miles is the farthest.

DR. BLESSING.—Is Giardia pathogenic to man?

DR. CHANDLER.—Yes, they may cause mild chronic diarrheas which clear up readily on administration of atabrin.

DR. HARVEY.—Are Parke-Davis chlorinating tablets effective in sterilizing water?

DR. CHANDLER.—They are all right but will not effect the amebic cysts.

QUESTION.—What is "Milton"? I have read of Englishmen in the tropics putting "Milton" in their tea.

DR. WILLIAMS.—"Milton" is a proprietary mixture of chlorine salts, which liberates chlorine when added to water. People in India used to add a few drops of this to their drinking water.

DR. CHANDLER.—A common source of infection with cholera and dysentery are fish, which are taken from polluted bodies of water and then eaten.

DR. BLATT.—Is there a decrease in the phage content of water during epidemics?

DR. CHANDLER.—Yes, at first there is a decrease. However, concurrent with the epidemic subsiding, there is a marked increase in the phage content of the water. The phage content of the Ganges water is so high that a glass of this water, if allowed to stand, will contain a decreasing number of organisms the longer it stands.

DR. WILLIAMS.—This may be the origin of the Indian custom of selling Ganges inhabitants water as a cure for illness.

DR. PERLSTEIN.—Is penicillium effective against dysentery?

DR. CHANDLER.—I do not know. However, vitamins play an important role. Patients who are debilitated and fail to respond to the ordinarily effective methods of therapy will frequently be cured by these methods when their vitamin intake is increased.

DR. WILLIAMS.—I am interested in hearing Dr. Chandler say that raising vitamin intake often clears up otherwise incurable cases of dysentery. This might work in resistant cases of malaria also.

DR. J. C. CARTER, INDIANAPOLIS.—Are we likely to see yellow fever from infected individuals after this war?

DR. ANIGSTEIN.—I do not think there is active danger unless the infected person comes to an area where *Aëdes aegypti* mosquito is present. After the third day of illness there is little danger of transmission.

DR. WILLIAMS.—Measures for control of yellow fever in this country are necessary because of the possibility of the *Aëdes aegypti* mosquito being carried in by planes arriving from infected areas.

DR. ANIGSTEIN.—Fumigation of such planes is now done.

DR. PERLSTEIN.—How is dengue diagnosed?

DR. ANIGSTEIN.—It is often difficult. It is caused by the same mosquito and has the same incubation period as yellow fever. Clinically, they may resemble each other also. However, the saddleback fever curve, leucopenia, absence of antibodies in the blood will serve to differentiate the two conditions. Immunologically they are distinct. Dengue has practically no mortality.

DR. GOODWIN.—Will you say something about jaundice caused by vaccination against yellow fever?

DR. ANIGSTEIN.—According to the official report, the outbreak of jaundice resembling the so-called "catarrhal jaundice" has occurred among our troops in various camps chiefly along the West Coast. The cases began to appear in March, 1942, the peak was reached in June, and since then there has been a steady decline.

The onset was gradual. Gastric and intestinal symptoms were prominent, fever was absent, jaundice the rule. The liver was enlarged in about 20 per cent of the cases. A total of 28,500 cases with sixty-two deaths was recorded. Death has usually occurred from two to six weeks after the onset.

The chief pathologic lesions were acute or subacute yellow or red atrophy of the liver, being distinctly different from the lesions of yellow fever.

Since all the men in the army units in which jaundice occurred had been previously vaccinated against yellow fever (total of over 1,500,000 men), the icterogenic factor was suspected to be present in the vaccine. The role of the virus itself could be easily eliminated (1) because the disease developed after an incubation period of from 70 to 120 days, and (2) because it has occurred in persons rendered immune to yellow fever. The search for the icterogenic agent resulted in incriminating the human serum component of the vaccine as responsible for these accidents. In consequence, human serum has been eliminated from the vaccine, and it is believed that the risk of jaundice can thus be avoided.

It is obvious from the above that nobody can be blamed for these purely accidental events, as it would be impossible to analyze every donor's serum for the presence of an icterogenic agent. Considering the total of 1,500,000 vaccinated persons, the jaundice developed in only 2 per cent, with a death rate of 0.2 per cent. This is negligible as compared with the danger of exposure to yellow fever infection should the immunization be abandoned.

DR. G. B. LOGAN, ROCHESTER, MINN.—What is the length of immunity artificially acquired, and are the Army and Navy repeating the vaccination?

DR. ANIGSTEIN.—Personally, I was vaccinated by the old method in 1936. Shortly after my blood showed immune bodies, but eight months thereafter another blood examination showed no immunity present.

Primarily jungle fever is a disease of the monkeys in the jungle and Findley found 20 per cent of the monkey blood samples sent from Africa to have immune bodies. Monkeys and opossums form the jungle reservoir for yellow fever.

The Pediatrician and the War

Maternity care for wives of service men and care for their infants will be available shortly throughout the Nation to those who apply for care to the State Health Departments, according to Katharine F. Lenroot, Chief of the Children's Bureau of the U. S. Department of Labor. Following appropriation by Congress of $1,200,000 to meet estimated need to July, plans are being rushed to extend such aid to women in the forty-eight States, Alaska, Hawaii, Puerto Rico, and the District of Columbia, she declared. The care will be available to the wife or the infant of any "buck" private, private first class, corporal, or sergeant in the Army and comparable grades in the Navy, Marine Corps, or Coast Guard. It is not eligible to wives of men in higher ranks. The twenty-eight States that already have approved plans will be able to extend their programs promptly, Miss Lenroot stated, and completion of arrangements in the remaining States should not require more than two or three weeks.

News and Notes

Because of a regulation of the War Production Board reducing the weight of paper for journals, it is necessary to print the JOURNAL on a lighter stock paper. While this will not affect the printed page, it will have some effect upon the quality of halftone illustrations. When these restrictions which are made necessary by the war are removed, the JOURNAL will return to the heavier type of paper used in the past.

THE EDITORS
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Book Reviews

Coming of Age. Esther Lloyd-Jones and Ruth Fedder, New York, 1941, Whittlesey House, 280 pages. Price, $2.50.

For young people of college age, and the more mature among high school students, the authors have written an eminently sane and surprisingly pleasant "know-yourself" book. It is representative of the better modern output in the field of social education. Not all psychology books by authors outside of the medical field are so gratifyingly free of errors in the medical matters included. Doctors, nurses, and parents, too, will find in this volume effective aid in constructive work with young people.

The writing is sprightly and clear although the subject be weighty. Some of the topics are: Personality Needs; Adjustments in Family Relationships; an excellent chapter on Men, Women, and Love; Effective Vocational Activity. A very acceptable and well arranged bibliography rounds out the book's reference value.

Though use is made in several chapters of a technique of short personal accounts of real life experiences, reason and conscious thinking are approached rather than one's emotional life aroused. The young people who would take to this book readily and complete its perusal would probably be those already possessed of considerable stability and thoughtfulness. The youngster in emotional difficulty might be discouraged by the jacket picture, depicting such obviously perfect and conventionally accepted youth and girl, right height, weight, hair, looks, dress and attainment of escort!

Nevertheless on the emotional aspects of the book something very good can be said: the approach is tolerant, nonpunitive, and permissive to the self-respect that is a necessary prelude to growing up and becoming responsible for oneself.

Though no book can actually stand in the place of trusted human advisors, they can aid, and *Coming of Age* would lend itself to group reading and discussion. It is in such approaches that the richest gains in orientation can be made. Human beings devise many techniques, song and story, revival meetings, books, bull sessions, and psychoanalysis, directed toward our irrefragable need for communication. More power to the creditable contact this book can make with those coming of age.

MacKaye.

The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects. John R. Paul, M.D., et al., for the American Heart Association, printed by the Metropolitan Life Insurance Company, ed. 2, 1943, 163 pages. Price on application.

In 1928 a study of environmental factors in rheumatic fever and rheumatic heart disease was undertaken by the American Heart Association. The results of this work were published in 1931 under the title, "The Epidemiology of Rheumatic Fever." Ten years later the Association has reviewed this subject in the light of many new developments which have transpired since the original was published for the purpose of bringing the work on the epidemiology of rheumatic fever up to date. This revision of the subject has been done again under the direction of a committee of the Association.

General information about this disease has increased so much and the point of view has changed so radically that the present review is not in reality a second

edition but rather a new monograph with a new title to indicate that, in addition to embracing the subject of the epidemiology of rheumatic fever, the work also includes some of its public health aspects.

Part One gives briefly the nomenclature and historic review of the subject and then discusses fully the relationships and the epidemiologic association of rheumatic fever with streptococcal infections. Part Two is more strictly confined to epidemiologic features of the disease, and Part Three gives, in general, the public health aspect. An appendix of particular importance in the pediatric field describes methods of determination of the incidence and prevalence of rheumatic fever; the technique of physical examinations for the determination of heart disease rates among school children; the rheumatic family; and the technique which has been used for morbidity surveys within small communities.

The appearance of this work coincides with the publication of a leaflet, *About Rheumatic Fever,* and a handbook, *The Recognition and Management of Rheumatic Fever and Heart Disease in Children,* both by the Metropolitan Life Insurance Company, and the inauguration of a health education program on rheumatic fever and heart disease with the American Heart Association, the Academy of Pediatrics, and the Crippled Children's Division of the Children's Bureau. This marks a notable period in the development of this disease. For the first time to a recognizable degree the emphasis has been placed on the occurrence of the disease in children, particularly as a point of attack for its control. Rheumatic fever and the results of heart disease have always been, and always will be, primarily a disease of young people, and, as the pediatric field embraces more and more the adolescent period, the disease will be of increasing importance to pediatrics. This implies that the pediatrician must be alert to his responsibility and ready to share in every phase of the problem. These several publications have been prepared with great care and will be the best available opinion on the subject.

McCULLOCH.